FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

ANTIVIRAL DRUGS ADVISORY COMMITTEE (ADVAC)

Thursday, April 28, 2011

8:00 a.m. to 4:00 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order and Introductions

DR. CARGILL: Good morning. I would first like to remind everyone present to please silent your cell phones, BlackBerry, any other devices you may have if you have not already done so. I would also look to identify the FDA press contact, Ms. Erica Jefferson.

There she is. Thank you, Erica.

Good morning. My name is Dr. Victoria Cargill. I'm the acting chair of the Antiviral Drugs Advisory Committee. I will now call the meeting of the Antiviral Drugs Advisory Committee to order.

We will go around the room and please introduce yourself. We will start with the FDA and Dr. Edward Cox to my left, and go around the table.

DR. COX: Good morning. Ed Cox, Director of the Office of Antimicrobial Products, CDER, FDA.

DR. BIRNKRANT: Debbie Birnkrant, Director of Division of Antiviral Products, FDA.

DR. LEWIS: Linda Lewis, medical team leader, Antivirals, FDA.

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DR. KORMAN: Louis Korman, gastroenterologist/hepatologist, Metropolitan Gastroenterology Group, Washington, D.C.

DR. KNODELL: Robert Knodell, gastroenterologist/hepatologist, Baltimore VA Medical Center and University of Maryland Medical School.

DR. CAMARDO: Joe Camardo. I'm head of Medical Affairs at the Forest Research Institute.

DR. CARGILL: Thank you.

There is one housekeeping detail before we begin. It's not on the agenda, but we will be taking a break this afternoon between 2:30 and 2:45.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without

interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Conflict of Interest Statement

MR. TRAN: Good morning. The Food and Drug Administration is convening today's meeting of the Antiviral Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of

1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with the federal ethics and conflict of interest laws, covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her

potential financial conflict of interest.

Under Section 712 of the Federal Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussions of new drug application, NDA 201-917, telaprevir, manufactured by Vertex, with a proposed indication for the treatment of chronic hepatitis C genotype 1

infection in combination with peginterferon and ribavirin in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.

This is a particular matters meeting during which specific matters related to Vertex's telaprevir will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

We would like to disclose that the consumer representative for the Antiviral Drugs Advisory Committee, Ms. Tracy Swan, is recused from participating in the discussions.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have made concerning the issues being discussed today.

With respect to the FDA-invited industry representative, we would like to disclose that

Dr. Joseph Camardo is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Camardo's role at this meeting is to represent industry in general and not any particular company. Dr. Camardo is employed by Forest Research Institute, a subsidiary of Forest Laboratories, Inc.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participant needs to exclude himself from such involvement, and that exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. CARGILL: Thank you.

We will now proceed with the FDA opening remarks from Dr. Debra Birnkrant. I would like to

remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Introduction/Background

DR. BIRNKRANT: Well, good morning, everyone. This is not exactly the right slide set for today, but it's the same theme as yesterday's. There should be a second set of slides. If not, I can just speak from notes.

MR. TRAN: I apologize.

DR. BIRNKRANT: Okay. No problem.

So today we'll be discussing the telaprevir NDA that was submitted under 201-917 by Vertex Pharmaceuticals. Telaprevir is an NS-34A protease inhibitor that was studied in combination with pegylated interferon and ribavirin in multiple populations. The trials assessed response-guided therapy, or RGT. When added to standard of care, higher SVR rates were seen.

In addition, there were higher SVR rates seen in difficult-to-treat populations. However,

their representation was limited, as you will see. There were additional toxicities when telaprevir was added to standard of care, that is, pegylated interferon and ribavirin, but these toxicities can be managed and monitored.

The FDA presentation will highlight the following. The clinical program will be summarized, including treatment duration in various populations. There will also be a limited resistance assessment, and there will be a limited discussion on IL28B. The second half of FDA's presentation will focus on safety.

Dr. Jadhav from our pharmacometrics group will discuss the premise that previous exposure to pegylated interferon and ribavirin appears to be less important than early virologic response in relation to RGT for prior relapsers.

Well, the positive thing about not having my slides here is that you don't have to look at the pipeline again.

[Laughter.]

DR. BIRNKRANT: But I will say it is still

full. And it's exciting today that we'll be talking about one of the direct-acting antivirals that is in the pipeline.

Our questions to the committee this afternoon relate to the safety profile of telaprevir, focusing on rash and anemia. The second question to the committee will be related to the risk-benefit of telaprevir, and that will be when the committee votes. Then there will be discussions related to efficacy and treatment duration in certain populations. And as before, we will ask about additional studies that need to be conducted.

The agenda is as follows. Following my remarks, Vertex Pharmaceuticals will present their data. This will be followed by a questioning period. After the break, FDA will make their presentation. This will also be followed by a period of questions for clarification purposes.

Lunch will take place around noon. This will be followed by an open public hearing at 1:00. Following the open public hearing, we'll have the

charge to the committee where we'll review the questions again. And then the committee can question or raise questions of the sponsor and the FDA. And then we'll go through the questions, take a vote, and conclude the meeting.

Thank you very much.

DR. CARGILL: Thank you.

We will now proceed with the sponsor presentations. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee

presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

Thank you.

Sponsor Presentation – Robert Kauffman

DR. KAUFFMAN: Thank you, Dr. Cargill.

Dr. Cox, Dr. Birnkrant, committee members, FDA staff, and guests, good morning. I'm Bob Kauffman, chief medical officer at Vertex Pharmaceuticals. On behalf of Vertex, it's a privilege to prevent the NDA for telaprevir for your consideration.

As you know, telaprevir is an inhibitor of the HCV protease. The indication under consideration this morning is as follows. Telaprevir is indicated, in combination with pegylated interferon and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis.

The indication includes patients who are treatment-naiçve and those who have been previously treated. These include prior null responders, partial responders, and relapsers.

Telaprevir has been in clinical development since 2004. Its extensive development program comprised more than 40 studies that are included in the NDA. Phase 3 development started in 2008, following a clinical advice meeting with FDA. We completed the rolling NDA submission in November of 2010. Notably, the safety database for telaprevir includes nearly 4,000 patients.

As you will hear today, hepatitis C is a significant public health problem. There is an

unmet need for treatment options that can increase sustained virologic response rates, or SVR, and reduce the treatment burden. Today we will present results of our comprehensive clinical development program in hepatitis C. Our data show that adding telaprevir to pegylated interferon and ribavirin produces substantial clinical benefit compared to the current treatment. This is exemplified by an SVR rate of 79 percent in treatment-naive patients.

Telaprevir's efficacy advantage is evident across subpopulations, including patients who have not achieved an SVR with prior therapy. Telaprevir also reduces treatment burden by reducing the treatment duration for up to two-thirds of treatment-naive patients, and our data show that patients with prior relapse can also benefit from response-guided therapy. The safety profile of telaprevir has been well characterized, and in our trials we implemented practical management strategies to protect patients.

Following this introduction, Dr. Ira Jacobson will present a brief background on the

burden of disease and the current treatment landscape of HCV. Then I'll provide an overview of the telaprevir clinical development program, focusing on early development.

Dr. Shelley George will discuss efficacy data from our Phase 3 program, followed by Dr. Priya Singhal, who will present the safety data. Then finally, I'll come back to the podium to summarize the benefit-risk assessment for telaprevir and offer some concluding remarks.

Following the presentation, we will be available to answer the committee's questions. In addition to Dr. Jacobson, we also have Dr. Robert Stern from Harvard with us to address questions as well.

Now I'd like to turn the podium over to Dr. Jacobson to discuss the current treatment landscape of HCV. Dr. Jacobson?

Sponsor Presentation – Ira Jacobson

DR. JACOBSON: Thank you, Dr. Kauffman.

Good morning. It's a privilege to appear before you today. I wish to disclose that I'm a

consultant and investigator for Vertex and have a similar relationship with Merck.

Following yesterday's excellent review by Drs. Birnkrant and Murray, I'd like to take just a few moments to provide a clinician's perspective on hepatitis C, a major public health problem for which there is a pressing need for improved treatment.

One hundred seventy million people globally are estimated to be infected with hepatitis C virus, or HCV. Three to four million people become infected annually, including tens of thousands in the United States. Genotype 1 HCV, the most difficult to treat, accounts for nearly three-quarters of all infections in the United States.

The magnitude of the public health problem posed by HCV is underscored by how much more common it is than HIV and hepatitis B virus in the United States. According to the recent report from the Institute of Medicine of the National Academy of Sciences, up to 75 percent of the 3 to 4 million Americans with hepatitis C have not even been

diagnosed yet. This presents a major public health challenge that needs to be addressed in parallel with the introduction of increasingly effective therapies.

Among the 70 to 75 percent of people who develop chronicity after acute infection, 10 to 20 percent develop cirrhosis after 20 years, and the incidence of cirrhosis continues to increase over the ensuing decades. Hepatitis C patients with advanced scarring, especially cirrhosis, have to live with the ever-present risk of liver cancer which may occur even in other well-compensated liver disease, along with the possibility of future decompensation and life-threatening complications.

Beyond the emotional burden imposed by the knowledge that one has hepatitis C, I'd like to share with you the problems faced by patients with cirrhosis. They frequently suffer from symptoms such as fatigue, weight loss, depression, muscle wasting, and impaired cognition. These symptoms decrease quality of life and may be disabling.

The most catastrophic complications of

advanced liver diseases include gastrointestinal bleeding, ascites, bacterial infections, encephalopathy, and liver cancer. Hepatitis C is the most frequent indication for liver transplantation in the United States. Although transplantation can be life-saving, recurrent hepatitis C in a transplanted liver may be associated with a rapidly progressive course.

Finally, as shown on the lower right of the slide, the mortality attributable to HCV in the United States is already substantial and expected to grow. According to a recent study, the prevalence of decompensated cirrhosis associated with hepatitis C in the United States began to increase after 1990, as shown on the left. In the absence of more effective therapy, the number of cases of decompensated cirrhosis is expected to increase to about 145,000 cases annually by 2020.

Similarly, the incidence of liver cancer in patients with hepatitis C and advanced fibrosis also began to increase after 1990. Should the risk of liver cancer in people with fibrosis remain

unchanged, the incidence of hepatitis C-related liver cancer is projected to peak in 2019 at about 14,000 cases per year.

A study published just this month from the VA HCV database affirms the increasing prevalence of cirrhosis and its complications among hepatitis C patients. In this database, perhaps the largest HCV database in the world, the prevalence of cirrhosis and decompensated cirrhosis more than doubled over a 10-year period, and the prevalence of liver cancer increased 19-fold. The rise in these prevalence rates remained highly significant after adjustment for gender and increasing age of the HCV cohort.

Of all cancers, liver cancer has the fastest-growing death rate in the United States, and the preponderance of this has been attributed to hepatitis C. From a personal perspective, hardly a week goes by in my practice without the detection of at least one new case of liver cancer in hepatitis C patients with advanced liver scarring who undergo regular screening.

At our weekly tumor boards, an alarming number of patients with liver cancer, the majority from hepatitis C, are presented to the team of specialists needed to provide optimal care for this often lethal condition.

Hepatitis C imposes a significant extrahepatic burden in addition to its better-known effects on the liver. For example, hepatitis C is associated with an increased risk of adult onset diabetes. This may be related to the inflammatory response induced by HCV, featuring up-regulation of cytokines which promote insulin resistance. A recent study showed a lower risk of subsequent diabetes in patients with sustained virologic response, or SVR, than in non-responders to a course of therapy.

Serious B cell proliferative disorders, including cryoglobulinemia and non-Hodgkin's lymphoma, arise more frequently in patients with hepatitis C. These B cell disorders may remit after HCV is eradicated. Patients with hepatitis C may suffer from diminished quality of life related

to such factors as depression and cognitive impairment, along with inflammatory disorders, including arthritis and Sjogren's syndrome.

These observations underscore that hepatitis C should be regarded as a systemic disorder. Successful treatment may reduce the impact of the extrahepatic manifestations of hepatitis C virus infection in addition to the burden of liver disease.

The ultimate successful treatment of a viral infection is viral eradication or cure. The biologic features of HCV, unlike those of HIV and hepatitis B, do indeed make it potentially curable. As shown on this slide, both HIV and HBV are able to archive or embed their genomes in forms that are not directly susceptible to currently available therapeutic agents, which effectively suppress viral replication but do not directly target archived viral genomes.

In contrast, there is no known archival form of the HCV genome. The implication of this is the ability to eradicate HCV with a finite course of

therapy. Consistent with this, over 99 percent of patients who have a sustained virologic response six months after completion of therapy remain free of detectible virus in the long term.

With the current standard of peginterferon and ribavirin, roughly 40 to 50 percent of patients with genotype 1 HCV have SVR, with the figures at the lower end predominating in the United States. Most genotype 1 patients require a full 48 weeks of therapy to optimize the chance of SVR.

Options in genotype 1 patients with prior treatment failure are very limited, with only about 10 percent of nonresponders, and, at most 25 percent of relapsers attaining SVR with retreatment. Many of our patients have been subjected to repeated courses of therapy to no avail.

Peginterferon and ribavirin therapy has a number of adverse effects. This leads to a shared hope among patients and physicians that with new agents, we can reduce the duration of therapy required to optimize the chance of cure. Factors

that adversely affect the chance of response to interferon include high viral load in genotype 1 patients, advanced liver scarring, older age, heavy body weight, and insulin resistance.

African Americans have lower rates of SVR than other ethnic groups. This has recently been explained, at least in part, by the discovery of polymorphisms in the region of the IL28B or lambda interferon 3 gene. These polymorphisms have a major impact on response to interferon.

For unknown reasons, persons of African heritage have a high prevalence of the T allele at the best-characterized of these loci, which is associated with nonresponse, whatever the ethnicity of the patient. In addition, about a third of HIV-infected persons have hepatitis C. Coinfection is associated with more rapidly progressive fibrosis and lower rates of response to treatment than monoinfection.

The benefits of SVR include improved histology, along with a reduction in several critical outcome measures, including

decompensation, de novo formation of varices, hepatocellular carcinoma, and actual mortality. Several studies support the contention that SVR improves outcomes in patients with hepatitis C.

The HALT-C trial was designed to study maintenance interferon therapy in patients with advanced hepatitis C who were nonresponders to previous treatment. They initially received full dose combination therapy with peginterferon and ribavirin, which was continued to 48 weeks if response occurred on treatment. In patients achieving SVR on this regimen, rates of compensation were significantly lower than nonresponders with respect to decompensated liver disease, transplantation, liver cancer, and liver-related death. The HALT-C trial is one of several studies indicating a sharp reduction in the incidence of liver cancer after SVR has been attained.

An important study from the VA system showed that SVR improves long-term survival. In nearly 17,000 patients who completed treatment no later

than mid-2008, SVR occurred in 35 percent of genotype 1 patients and in higher numbers of those with genotypes 2 or 3. Multivariate modeling accounting for a wide variety of comorbidities common in this population demonstrated an association between SVR and a highly significant reduction in all-cause mortality.

With new antiviral agents, we can look forward to a significant improvement in the rate of SVR in genotype 1 patients. By tailoring the duration of therapy according to the kinetics of response, a concept known as response-guided therapy, we expect to shorten the duration of therapy in a much larger proportion of patients than is currently possible.

Cure of infection in more patients should prevent many life-threatening complications of hepatitis C and reduce the need for transplantation. We need to reverse the rising tide of morbidity and mortality and reduce the human toll taken by this disease.

Now I'd like to invite Dr. Kauffman back to

the podium to provide an overview of the sponsor's clinical development program. Thank you.

Sponsor Presentation – Robert Kauffman

DR. KAUFFMAN: Thanks, Dr. Jacobson. And now let's turn our attention to the telaprevir development program. I'll touch on a few important aspects of clinical pharmacology and virology and then discuss the key learnings from our Phase 1 and 2 studies that guided Phase 3 development.

As you've heard, telaprevir is an orally bioavailable inhibitor of the hepatitis C virus protease. In in vitro studies, it has demonstrated reversible and tight binding to the HCV protease active site. It forms a stable enzyme inhibitor complex with a long half-life of about one hour. The inhibition constant of this stable complex is 7 nanomolar. Telaprevir has an IC50 in the replicon system of 350 nanomolar, concentrations that are readily exceeded in vivo.

The goals of our clinical development program were to increase SVR rates for both treatment-naive and treatment-experienced patients

and to shorten treatment duration where appropriate. To achieve these goals, Vertex has conducted a broad clinical program comprising five Phase 2 studies and three Phase 3 studies.

This program was supplemented by a clinical pharmacology and virology program to characterize the pharmacokinetics and pharmacodynamics of telaprevir to evaluate for drug-drug interactions and to understand the potential for viral resistance. The integrated data from these studies provided key information on the dose and duration of each of the components of the treatment regimen.

Here I'm providing the highlights of the clinical pharmacology program for telaprevir. Telaprevir has a plasma half-life of 9 to 11 hours at steady state. Food substantially increases bioavailability, so telaprevir must be administered with food.

Telaprevir is metabolized by both CYP3A4 and non-CYP mechanisms and is excreted primarily through the GI tract. It's notable that telaprevir plasma concentrations are not substantially

increased by metabolic inhibition at steady state, providing a safety factor during co-administration with other drugs.

We have conducted a comprehensive clinical pharmacology program that has thoroughly characterized the potential for drug-drug interactions with telaprevir. Telaprevir is a substrate and potent inhibitor of CYP3A and a substrate of PGP. Telaprevir may saturate or inhibit PGP in the GI tract. In these respects, it's similar in its drug interaction potential to some HIV protease inhibitors you may be familiar with.

We evaluated the drug-drug interactions of telaprevir with many drugs commonly used in patients treated for hepatitis C, and these are listed here. There is an interaction with the estrogen component of oral contraceptives that may reduce their effectiveness.

We also evaluated antiviral drugs used in HIV as well as immunosuppressive agents and drugs used by patients with opioid dependency. Two

additional studies are ongoing and their clinical phase is complete, and these are studies of interactions with raltegravir and buprenorphine. These data will provide important information for prescribing physicians.

We have also studied the clinical pharmacology of telaprevir in special populations. Mild hepatic impairment has minimal impact on telaprevir pharmacokinetics. Notably, in patients with moderate hepatic impairment, plasma concentrations of telaprevir are reduced by 46 percent. In a single-dose study, severe renal impairment did not have a substantial effect on telaprevir pharmacokinetics.

To further characterize the PK in special populations, we are collecting PK data in our ongoing coinfection study, and we are planning a study in people with recurrent hepatitis C after liver transplantation.

To identify the appropriate dose of telaprevir, we evaluated viral dynamics, both in monotherapy and in combination therapy. The first

viral dynamic study evaluated three dose levels of telaprevir alone over 14 days. I draw your attention to the very rapid initial decline in HCV RNA for all dose groups. Note also the more consistent decline at the 750-milligram dose level shown in orange. These data, along with the results of concentration effect modeling, led us to select 750 milligrams are the clinical dose.

The figure on the right shows the viral kinetics for peginterferon alone, and for telaprevir with and without coadministration with peginterferon. Telaprevir has about a 1,000-fold greater antiviral compared to peginterferon. You'll note the pattern of viral decline for telaprevir monotherapy in the second study was the same as seen in the first study, and these are the lines in orange. But with co-administration, an even greater rate of decline is shown, as seen in the pink line, because co-administration also inhibits telaprevir-resistant variants.

HCV exists in infected individuals as a genetically diverse viral population due to its

rapid, error-prone replication. This means that drug-resistant variants preexist and can be selected by the antiviral agent. Across our program, we have conducted an analysis of viral variants, representing sequences from over 3400 patients at baseline, and in 740 patients who did not achieve an SVR.

The resistance profile has been found to be consistent across patient populations. Overall, 12 to 22 percent of all patients starting treatment have had detectible resistant variants after treatment failure. Follow-up studies have shown that resistant variants tend to diminish over time in the absence of treatment, and Dr. George will provide more information on this topic in her talk that follows mine.

To define telaprevir's resistance profile, we performed sequence analyses in patients who did not have an SVR. We consistently detected substitutions at four positions in the NS3 protease region, and those are positions 36, 54, 155, and 156. The double variant, V36M plus R155K, is also

commonly found.

Variants are shown here in increasing degree of resistance from left to right. It's important to note that all variants were less fit than wild type, providing a mechanism by which they diminish in frequency over time in the absence of drug-selected pressure. There is cross-resistance among different protease inhibitors. However, all variants are sensitive in vitro to other classes of antiviral agents and to peginterferon and ribavirin.

One of the topics we'll discuss today is the use of response-guided therapy. With response-guided therapy, treatment duration is determined by the rate of viral decline. Let me show you how the combination of viral dynamic modeling and empirical data were used to help estimate the treatment duration for achieving SVR in our trials.

To achieve an SVR, the total body burden of viable virus needs to be below one copy, which is represented here by the black dashed line. The blue horizontal line shows the limit of

quantification of the RNA assay. This means the virus is undetectable once it falls below this line; but of course it may still be present.

The typical response to peg and ribavirin is shown here in red. It indicates the current 48-week duration of treatment to achieve an SVR. Only a single line is indicated because there is no known virologic resistance to peg and ribavirin.

With telaprevir-based therapy, total body eradication requires elimination of both wild type and resistant variants. They are represented here by the purple and green lines. This rate is much faster, on average, for a telaprevir regimen compared to peg and ribavirin.

Through an evaluation of the time to eradication of wild type virus and viral variants and empirical data from the Phase 2 program, we estimated durations of treatment necessary for complete viral eradication. These hypotheses were then tested in subsequent clinical trials.

In Phase 2, we sought to answer several basic questions necessary to further advance the

program. The primary results of those studies are summarized here. With respect to patient populations, we demonstrated efficacy in both treatment-naive and treatment-experienced patients. With respect to safety, we encountered severe rash for the first time and implemented successful management strategies for rash and for anemia.

The dose was based on Phase 1 data, as I've shown you a few moments ago, and PK/PD modeling, and was subsequently reconfirmed with PK/PD analyses of safety and efficacy. The 12-week duration of telaprevir was based on Phase 2 data and was supported by viral modeling. There was no demonstrable advantage to more than 12 weeks of telaprevir.

With respect to the treatment regimen, in Phase 2 we demonstrated that the absence of ribavirin in the regimen substantially increased breakthrough and relapse rates, and, therefore, ribavirin has been shown to be a key component of the regimen.

The potential of response-guided therapy was

demonstrated in treatment-naive patients with 61 to 69 percent SVR rates and low rates of relapse with 24 weeks of treatment.

I'll now turn the podium over to Dr. Shelley George, who will show you how these concepts were incorporated into the Phase 3 program and the outcome of those studies.

Sponsor Presentation – Shelley George

DR. GEORGE: Thank you, Dr. Kauffman.

Good morning. I am Shelley George, vice president, HCV Therapeutic Area Lead in Medical Affairs at Vertex. It is a privilege to present the telaprevir Phase 3 efficacy data today.

As you have heard from Dr. Jacobson, sustained viral response, or SVR, is considered to be a virologic cure in HCV-infected patients. However, the standard treatment of pegylated interferon and ribavirin, or PR, for 48 weeks, leaves 50 to 60 percent of genotype 1 treatment-naive patients without a cure, and there are limited options for successful retreatment. Given these limitations, increasing SVR rates and

shortening treatment duration were important goals for the telaprevir Phase 3 development program.

I will start my talk by reviewing critical design features shared by all of the Phase 3 studies. These studies were designed to assess the efficacy and safety of 12 weeks' treatment with telaprevir, 750 milligrams thrice daily, in combination with either 24 or 48 weeks of pegylated interferon and ribavirin, according to the package insert, based on treatment response.

The Phase 3 studies included both treatment-naive and treatment-experienced patients with genotype 1 chronic hepatitis C. Enrolled patients had varying degrees of liver disease, including compensated cirrhosis. They were from different geographic regions and had diverse racial and ethnic backgrounds.

The primary endpoint in all three of the studies was the proportion of patients achieving SVR, defined as having undetectable HCV RNA levels 24 weeks after the last planned dose of study drug. This endpoint is more conservative than the last

actual dose because it requires a longer follow-up period for patients who prematurely discontinue treatment.

Now, each of the Phase 3 studies also had unique features, such as response-guided therapy and lead-in dosing. These features were designed to address issues vital to the recommended treatment protocol. Study 108, known as ADVANCE, was a pivotal Phase 3 study designed to establish the superiority of telaprevir in combination with peg/ribavirin compared with the standard regimen in treatment-naive patients.

The duration of PR treatment was determined using a response-guided approach with the following criteria. Patients with undetectable HCV RNA at weeks 4 and 12 of treatment, known as an extended rapid viral response, or eRVR, had a planned treatment duration of 24 weeks of pegylated interferon and ribavirin. Those who did not achieve an eRVR had a planned treatment duration of 48 weeks of pegylated interferon and ribavirin. In this study only, both 8-week and 12-week telaprevir

treatment durations were evaluated.

Moving on to study 111, or ILLUMINATE, this was a supportive phase 3 study designed to confirm response-guided therapy in treatment-naive patients. The third study, C216, known as REALIZE, was a pivotal phase 3 study designed to establish the superiority of a telaprevir-based regimen among treatment-experienced patients, including prospectively defined prior relapses, prior partial responders, and prior null responders. A unique feature of this study was the inclusion of an arm with a 4-week lead-in with PR before commencing telaprevir treatment.

Now I will review the highlights of pivotal study 108, ADVANCE. This was a randomized, double-blind, placebo-controlled, multicenter study. Patients were randomized to one of three treatment groups in a 1 to 1 to 1 ratio, stratified by HCV genotype and baseline viral levels.

Telaprevir was given in combination with PR for either the first 8 weeks, noted here as T8/PR, or for the first 12 weeks, shown as T12/PR.

Patients in the 8-week telaprevir group received telaprevir-matched placebo during weeks 9 through 12. Patients who achieved an extended rapid viral response, eRVR, had a planned pegylated interferon and ribavirin treatment duration of 24 weeks. Those who did not achieve eRVR had a planned PR treatment duration of 48 weeks.

For the control group, the total treatment duration was 48 weeks, with telaprevir-matching placebo given for the first 12 weeks and peg/ribavirin dose for the entire 48-week period. All patients were followed to week 72 for a common assessment time point.

The patient demographics and baseline characteristics in the study were well-balanced across the treatment groups. Notably, 60 percent of sites were located in North America, and 40 percent of sites were located in Europe and other countries. Factors associated with a poor response to peg/ribavirin therapy include black or African American or Hispanic or Latino race or ethnicity, high baseline viral levels, and more

advanced liver disease.

Of the 1,088 patients who received at least one dose of study drug, 9 percent of patients enrolled in this study were black or African American and 11 percent were Hispanic or Latino. The majority of patients in each of the three treatment groups had high baseline viral levels, 15 percent of patients had bridging fibrosis, and 6 percent had cirrhosis.

Sustained viral response rates were markedly and significantly higher in the telaprevir-treated groups as compared with the standard treatment group. In the 12-week telaprevir group, the SVR rate was 79 percent as compared with 46 percent in the standard treatment arm, an absolute significant difference of 33 percent. In the 8-week telaprevir group, the SVR rate was 72 percent, an absolute significant difference of 26 percent as compared with standard treatment. The SVR rate of 46 percent in the control arm was similar to that reported in the literature.

The proportion of patients who achieved SVR

was higher in the 12-week telaprevir group than the 8-week telaprevir-treated group. This study was not designed to compare response rates across the two telaprevir regimens. However, a numerical difference of 7 percent was observed in favor of the 12-week telaprevir-treated group, with a confidence interval which lies entirely to the left of zero. These efficacy results favor the T12 regimen.

Fifty-eight percent of patients in the study who received a telaprevir-based regimen achieved an extended rapid viral response, or eRVR. These patients were therefore eligible for a planned total treatment duration of 24 weeks. In contrast, only 8 percent of patients achieved eRVR in the control group, and these patients were assigned to receive 48 weeks of treatment per protocol.

eRVR status is a critical factor in determining treatment outcome. SVR rates were high, ranging from 87 percent to 92 percent, in eRVR-positive patients who received 24 weeks of treatment with a telaprevir-based regimen. SVR was

also high among eRVR-positive patients in the control group, who received 48 weeks of treatment per protocol. However, as we've seen in the previous slide, only 8 percent of patients in the control group achieved eRVR.

By contrast, SVR rates ranged from 52 percent to 60 percent among those patients who did not achieve eRVR and received 48 weeks of treatment with a telaprevir-based regimen. These SVR rates were higher than those achieved by patients who did not achieve an eRVR in the control group, indicating that telaprevir confers benefit for a proportion of these patients as well.

Overall, relapse rates among telaprevir-treated patients were low, notably, three- to fourfold lower than with standard treatment. Low relapse rates were observed among those patients who achieved eRVR. High SVR rates and low relapse rates observed in patients who achieve eRVR indicate that shortening the duration of therapy did not compromise treatment outcomes in these patients.

SVR rates were higher in the telaprevir-treated groups than in the control group regardless of baseline demographics and disease characteristics. This forest plot shows the absolute differences and the 95 percent confidence interval for the differences in SVR rates by baseline characteristics between the 12-week telaprevir-treated group and the control group.

Substantial clinical benefit was achieved across a broad range of patient subgroups, including some groups that traditionally have a worse outcome with standard treatment. These include black, African American, and Hispanic or Latino patients, and those with cirrhosis or high baseline HCV RNA levels. In some subgroups, such as age greater than 65 years, HCV genotype 1, subtype unknown, the low number of patients resulted in wide confidence intervals.

Telaprevir-based regimens provided a substantial benefit regardless of the stage of liver disease. Patients with less advanced liver disease had higher response rates than patients

with bridging fibrosis or cirrhosis. However, the substantial treatment difference observed between the telaprevir-treated groups and the control group was maintained regardless of the stage of liver disease.

SVR rates were substantially higher in the telaprevir-treated groups than in the control group across the races and ethnicities shown here. Hispanic or Latino patients treated with a 12-week telaprevir regimen achieved an SVR rate of 77 percent, similar to the 79 percent SVR rate achieved in Caucasian patients. Black or African American patients treated with a 12-week telaprevir-based regimen achieved an SVR rate of 62 percent, as compared with 25 percent for the standard treatment group. Importantly, the substantial treatment difference between the telaprevir-treated groups and the control group was maintained across all subgroups shown here.

In conclusion, this study in the treatment-naive patient population demonstrated the clinical benefit of telaprevir, with an absolute significant

difference of 33 percent in SVR rates for the 12-week telaprevir-based regimen compared with standard treatment.

Clinical benefit was achieved across a broad range of patient subgroups, including those that are difficult to cure with standard treatment such as blacks and African Americans, Hispanics or Latinos, and patients with cirrhosis. High SVR rates and low relapse rates support a 24-week treatment duration in those patients who achieve an eRVR.

Now I will move on to study 111, known as ILLUMINATE. This noninferiority study was designed to support pivotal study 108, with a goal of confirming response-guided therapy among treatment-naive patients. As you have seen in study 108, high SVR rates were achieved among patients who achieved an eRVR and those received a treatment duration of 24 weeks. Study 111 is designed to answer the question of whether or not there is clinical benefit in extending peg/ribavirin treatment duration from 24 weeks to 48 weeks among

those patients who achieve an eRVR.

This was a randomized, open label, multicenter study. Telaprevir was administered in combination with PR for 12 weeks. The total duration of PR treatment was either 24 or 48 weeks. Those patients who achieved eRVR and completed the week 20 visit were randomized in a 1 to 1 ratio to either stop all study treatment at week 24 or to continue treatment with PR to week 48. Those patients who did not achieve eRVR were assigned to receive treatment with PR for 48 weeks.

Patients who received at least one dose of study drug but who prematurely discontinued treatment before week 20 were not randomized or assigned to a treatment regimen. All patients were followed to week 72.

Study 111 was designed to determine if extending the PR treatment duration from 24 to 48 weeks in those patients with eRVR would result in additional benefit. Therefore, the primary focus of this presentation will be on the randomized eRVR-positive treatment arms.

The primary comparison was based on confidence interval estimates to rule out the inferiority of the 24-week regimen to the 48-week regimen among those patients who achieved eRVR. The predefined noninferiority margin was 10.5 percent. Of note, although this was an open label study, HCV RNA levels from tests prior to week 24 and eRVR status were not revealed to the investigator or patient until the end of the study. This was intended to reduce the potential for bias among those patients who received 48 weeks of therapy in the study.

Patient demographics and baseline characteristics were similar among the randomized treatment groups and generally representative of the overall study population. Notably, 94 percent of sites were located in North America. In the overall study population, 14 percent of patients enrolled were black of African American and 10 percent were Hispanic or Latino. The majority of patients had high baseline viral levels, and of the 540 patients enrolled, 16 percent had bridging

fibrosis and 11 percent had cirrhosis.

SVR rates in the randomized eRVR-positive arms were 92 percent for the 24-week treatment group and 90 percent for the 48-week group. The lower limit of the two-sided 95 percent confidence interval on the difference in SVR rates between the two groups was minus 4.3 percent, to the right of the predefined noninferiority margin of minus 10.5 percent, confirming that 24 weeks of treatment is not inferior to 48 weeks of treatment.

Overall, 65 percent of patients in the study achieved an extended rapid viral response. The SVR rate in the study overall was 74 percent, similar to the response rate observed in study 108.

In conclusion, study 111 confirms the use of response-guided therapy in treatment-naive patients treated with telaprevir. There was no evident advantage in extending treatment for 48 weeks as compared with 24 weeks in those patients with eRVR. The treatment outcome in the study is very similar to that of pivotal study 108.

Next I will review the results of pivotal

study C216, known as REALIZE. This study was designed to confirm the superiority of telaprevir in combination with PR, as compared with PR alone, among those patients who did not achieve a sustained viral response after a prior course of PR therapy. This study also included an arm containing a 4-week lead-in with peg/ribavirin prior to starting telaprevir to assess the potential impact of a lead-in on treatment outcomes.

Patients in this study were prospectively studied with predefined, well-documented, prior nonresponse criteria. The definitions of populations in this study were in accordance with the FDA draft HCV guidance. Patients had either prior relapse, defined as HCV RNA undetectable at the end of a prior course of PR therapy but not achieving SVR, or prior nonresponse, defined as never having had an undetectable HCV RNA level during or at the end of a prior course of PR therapy.

Prior nonresponse was further categorized as

either partial response, greater than a week or 2 log decrease in HCV RNA at week 12, or null response, less than a 2 log decrease in HCV RNA at week 12. Patients with prior null response are the most difficult to cure, with SVR rates ranging from naught to 10 percent after retreatment with pegylated interferon and ribavirin.

REALIZE was a randomized, double-blind, placebo-controlled study. Patients were randomized in 2 to 2 to 1 ratio to one of three treatment groups, all with a planned treatment duration of 48 weeks. In the first treatment group shown above, patients received telaprevir in combination with PR for 12 weeks, followed by placebo plus PR for 4 weeks, then followed by PR for an additional 32 weeks.

In the next group, the lead-in group, patients received placebo in combination with PR for 4 weeks, followed by telaprevir plus PR for 12 weeks, followed by PR for an additional 32 weeks once again.

In the standard treatment group, patients

received placebo plus PR for 16 weeks, followed by PR for 32 weeks. At the end of treatment, all patients were followed until 24 weeks after the last planned dose of study drug.

Demographic and baseline disease characteristics were comparable in this study across the treatment groups. Importantly, 60 percent of sites in this study were located in Europe and 40 percent were located in North America and other countries. Five percent of enrolled patients in the study were black or African American, and 11 percent were Hispanic or Latino.

Of the 662 patients treated, there was a high proportion of patients with poor prognostic factors. The majority of patients had high baseline viral levels across the treatment groups; 18 percent of patients were prior partial responders, and 27 percent were prior null responders, the hardest patients to cure; 22 percent had bridging fibrosis, and 26 percent of patients had cirrhosis. Not shown here, but of note, the proportion of patients with cirrhosis was

higher in the prior nonresponder population than in the prior relapser population.

Among prior relapsers, SVR rates in the telaprevir treatment groups were significantly and markedly higher than the control group. SVR rates were 84 percent and 88 percent in the immediate start and lead-in telaprevir groups respectively, as compared with 22 percent in the control group. SVR rates were similar in the two telaprevir-treated groups, with and without a lead-in.

For prior null responders and prior partial responders, the SVR rates were also significantly higher in each of the telaprevir treatment groups than in the control group. Among prior partial responders, SVR rates were 61 percent and 56 percent in the immediate start and lead-in telaprevir-treated groups, as compared with 15 percent in the control group. Among prior null responders, SVR rates were 31 percent and 33 percent in the immediate start and lead-in telaprevir-treated groups, as compared with 5 percent in the control group. Once again, SVR

rates were similar in the two telaprevir-treated groups with and without a lead-in.

Treatment outcomes were similar across the subgroups in the arms with and without a lead-in. Among prior relapses, virologic failure, shown here in purple, occurred rarely and relapse rates, shown here in aqua, were low. Among the prior nonresponders, virologic failure and relapse occurred more frequently and were highest among the prior null responders.

On-treatment virologic failure and relapse rates were similar between the two telaprevir-treated therapies with and without a lead-in. There was also no difference in the types of emerging viral variants between the two groups.

This forest plot shows the absolute differences in SVR rates between the 12-week telaprevir-treated groups and the control group, and the 95 percent confidence interval for the difference by subpopulations. SVR rates were higher in each telaprevir group than in the control group in Caucasian patients. However, the number

of patients in other subgroups by race was too low to allow a meaningful comparison across the subgroups.

Subpopulations with wide 95 percent confidence intervals reflect small sample sizes, seen in patients over 65 years old, those of black race and Asian race. Among prior relapsers and prior nonresponders, SVR rates were higher in the telaprevir groups than in the control group by baseline disease characteristics such as HCV subtype, HCV RNA levels, and liver disease status.

The SVR rates for the pooled telaprevir groups in the study were significantly higher than for retreatment with PR alone in all subpopulations; for prior relapsers, 86 percent versus 22 percent in the control group; prior partial responders, 59 percent versus 15 percent in the control group; and prior null responders, 32 percent versus 5 percent in the standard treatment group. SVR rates, virologic failure, and relapse rates were similar between the two telaprevir-treated groups with and without lead-in.

Response-guided therapy was not prospectively evaluated in the treatment-experienced population in the study. However, data from Phase 2 and 3 studies indicates that the treatment-experienced patient population is not uniform. In fact, patients with prior relapse appear to be more similar to the treatment-naive patient population than to the prior nonresponse population based on both rapidity of the antiviral response on treatment and the SVR rates.

Data analyses indicate that patients with prior relapse are likely to benefit from response-guided therapy. This is based on the same criteria as for treatment-naive patients, undetectable HCV RNA at weeks 4 and 12 or eRVR. These data analyses are further supported by viral dynamic modeling.

I will now briefly review the clinical evidence supporting response-guided therapy in prior relapses from Phase 2 and Phase 3 studies. The majority, 58 to 96 percent, of patients in both the prior relapse and treatment-naive patient populations achieved eRVR, shown here in orange.

Let's now look at the blue bars, which show SVR rates among eRVR-positive patients, starting on the left-hand side with the treatment-naive subpopulation. SVR rates of 92 percent were achieved by treatment-naive patients with eRVR who were treated for 24 weeks in study 108.

Similar SVR rates, ranging from 89 percent to 100 percent, were achieved by eRVR-positive patients with prior relapse who were treated for 24 weeks in the Phase 2 studies 106 and 107, shown in the center. These high response rates were comparable to the SVR rate of 96 percent achieved by eRVR-positive prior relapses who received 48 weeks of treatment per protocol in study C216.

In summary, both prior relapsers and treatment-naive patients represent populations with high interferon responsiveness, and in both these patient populations, patients with eRVR achieve high SVR rates. Of note, SVR rates were high in prior relapses regardless of the duration of pegylated interferon and ribavirin. This suggests that achieving eRVR was the critical factor in

determining outcome. These results were further confirmed by viral dynamic modeling, and taken together, support response-guided therapy among prior relapsers.

Now we'll move on to the durability of response achieved with a telaprevir-based regimen. This was investigated in two settings, firstly, in patients who had achieved an SVR during the one-year follow-up period in the Phase 2 clinical studies, and secondly, in an ongoing three-year observational follow-up study known as study 112, or EXTEND.

Relapse after achieving an SVR with standard PR therapy occurs in less than 1 percent of treated patients. Durability of response for telaprevir was assessed in 361 patients who had achieved an SVR after treatment with a telaprevir-based regimen in a phase 2 study. Patients were also required to have had at least one post-SVR follow-up assessment.

Two patients had late relapse within six months after achieving SVR during the study follow-

up period. All other patients with SVR, who have been followed up for three years after end of treatment, continue to have undetectable HCV RNA.

Study 112 is an ongoing observational three-year follow-up study to evaluate the durability of response in a cohort of patients with SVR following telaprevir-based treatment in a prior trial. Patients were given the option to enroll in this follow-up study, which was initiated during the course of the Phase 3 program. The current interim analysis included 123 patients with SVR in a phase 2 study. Patients in the Phase 3 studies had not been enrolled at the time of this analysis.

Durability of response was demonstrated in 122 of 123 patients, who were followed for 5 to 35 months after SVR, with a median follow-up time of 22 months. One patient had late relapse before he enrolled in study 112. This is the same patient that was previously reported during the follow-up period in Phase 2. No late relapses have occurred during the observational period of study 112, which is ongoing.

Now I'd like to move on to the evolution of resistant variants after treatment in patients who did not achieve an SVR in a prior trial. This was studied during the Phase 3 program, with a median follow-up period of about one year after treatment failure. In addition, an interim analysis of study 112 has been conducted with a median follow-up period of about two years. I will start with an analysis of patients from the Phase 3 trials.

Of those patients in Phase 3 trials who did not achieve an SVR, 84 percent of those patients with genotype 1A and 54 percent of those patients with genotype 1B had detectable resistance after treatment failure. The rates and median time to loss of detectable resistant variants by population sequencing was estimated with a Kaplan-Meier curve. There was a difference between subtypes, with a median time of 10 months for genotype 1A patients and 3 weeks for genotype 1B patients.

These results suggest that resistant variants were no longer detected by population sequencing over time in both treatment-naive and

treatment-experienced patients. Notably, about one-quarter of these patients were prior null responders.

Study 112 was also designed to evaluate changes in HCV variants over time in a separate cohort of patients without SVR following telaprevir-based treatment in a prior trial. For the purpose of this interim analysis, patients were required to have both detectable telaprevir-resistant variants at the post-nadir time point in the previous trial and viral sequencing data available from study 112.

Of the 56 treatment-naive and treatment-experienced patients from the Phase 2 program, almost 90 percent of patients, 50 of 56, no longer had detectable resistant variants by population sequencing, with a median follow-up time of about two years. We will continue to follow all patients after three years.

To further confirm the loss of resistant variants, a more sensitive clonal sequence analysis was performed on a subset of patients from

study 112. These results show that viral populations at follow-up were not enriched in resistant variants as compared with baseline. As there is no data yet on retreatment of these patients, the clinical implications of this finding are not known. However, these emerging data are encouraging.

In conclusion, interim data from study 112 have demonstrated that sustained viral response with telaprevir is durable. Late relapse is rare and consistent with historical late relapse rates with PR of about 1 percent. In those patients who did not achieve an SVR after telaprevir treatment, emerging data suggest that the frequency of resistant variants declines over time.

Now I will close my talk with the overall efficacy conclusions from the telaprevir Phase 3 program. Telaprevir-based regimens resulted in significantly higher SVR rates in both treatment-naive and treatment-experienced patients as compared with standard treatment. This clinical benefit was observed across a broad range of

patients, including subgroups associated with a poor response to peg/ribavirin. Similar treatment outcomes were achieved in treatment-experienced patients with and without a 4-week PR lead-in.

Response-guided therapy enabled the majority of treatment-naive patients to achieve high SVR rates with 24 weeks total therapy. Phase 2 and 3 clinical data and viral dynamic modeling support response-guided therapy in those patients with prior relapse to PR treatment.

Thank you for your attention. I would now likewise to invite Dr. Singhal to the podium to address the safety profile of telaprevir.

Sponsor Presentation – Priya Singhal

DR. SINGHAL: Thank you, Dr. George.

Good morning. I'm Priya Singhal, senior director, Disease Area Safety Lead, Vertex Global Patient Safety. I will present telaprevir safety.

I'll start with a review of general safety. Following that, I'll discuss analyses performed for specific adverse events, along with their respective management during the Phase 3 program.

Then I'll close with overall conclusions.

Before we begin our review, I'd like to draw your attention to the following important considerations. Telaprevir is added for the first 12 weeks of a total 24- or 48-week regimen of peginterferon and ribavirin, also referred to as PR. Peginterferon and ribavirin have a well-characterized safety profile. Adverse events such as anemia, rash, fatigue, and fever are common.

These PR-associated adverse events also occur in the first 12 weeks when telaprevir is being dosed. However, these adverse events continue to have a significant prevalence until the peginterferon and ribavirin dosing is completed.

Telaprevir's safety profile has been similar across the treatment-naive and the prior treatment-experienced patients. The safety profile was also similar across the Phase 2 and 3 studies. Hence, safety data were pooled across the Phase 2 and 3 studies. Details of these analyses are in your briefing document. Today's presentation will focus on the pooled safety data from the Phase 3 studies

alone.

Let's start with general safety. More than 3,800 patients across the entire clinical development program have been exposed to telaprevir. As Dr. George just discussed, there were a total of three Phase 3 studies. Two of these studies included genotype 1 HCV treatment-naive patients, and one included prior treatment-experienced patients, all with compensated liver disease.

A total of 1797 patients were randomized to any telaprevir/peginterferon/ribavirin combination regimen, and 493 to placebo, peginterferon, and ribavirin combination regimen. Unless mentioned otherwise, I will present data from the telaprevir/placebo phase. In the placebo-controlled studies, this was the period during which patients received either telaprevir or placebo in combination with peginterferon and ribavirin.

This here is an overview of patient disposition and key reasons for discontinuation.

Across Phase 3, 71 percent of patients randomized to telaprevir combination treatment groups completed, compared with 51 percent of patients in peginterferon and ribavirin groups alone.

Now, as you look at reasons for discontinuation, you can see an additional 4.7 percent of telaprevir-treated patients did not complete due to an adverse event. No deaths occurred during the telaprevir combination treatment, and one occurred during the peginterferon and ribavirin treatment.

Upon reviewing adverse events, we observed that almost all patients in both groups, 96 percent or more, experienced an adverse event regardless of whether they received telaprevir or placebo. This is reflective of the adverse events associated with peginterferon and ribavirin.

Reviewing other indicators, you can see in the left column that when telaprevir is added to peginterferon and ribavirin, there is a higher incidence of serious adverse events grade 3 or severe adverse events and adverse events leading to

treatment discontinuation.

Next we will review adverse events in patients receiving telaprevir combination treatment as compared with placebo plus peginterferon and ribavirin. We'll start by looking at the most common AEs. These here are the adverse events that occurred in at least 20 percent of patients in either group. Now, fatigue, pruritus, nausea, rash, anemia, and diarrhea occurred at a 5 percent greater incidence in the telaprevir combination group.

Now let's review adverse event severity. These are the AEs that were reported as grade 3 or severe in 1 percent or more patients in either treatment group. Of these, anemia, fatigue, and rash were reported at a 1.5 percent greater incidence in the telaprevir combination group. Anemia and rash were also the events that led to a higher discontinuation rate in the telaprevir combination group as compared with placebo/peg/ribavirin.

Next we will review specific analyses for

rash and anemia and the management of these events in the Phase 3 program. Let's begin with a review of rash.

Severe rash was first reported in the Phase 2 program. In response, a rash assessment and management plan, including severity grading and general guidance was implemented to ensure patient safety. In Phase 2, a severe rash required all study drugs to be discontinued. Based on the Phase 2 experience, management of severe rash was modified in Phase 3 to require that telaprevir alone be discontinued. Importantly peginterferon and ribavirin could be continued per clinical judgment. In addition, an external rash adjudication panel was appointed to characterize severe rash. This panel was chaired by Dr. Robert Stern from Harvard Medical School, who's here with us today.

In parallel with these activities, several investigations were undertaken to try and understand the rash etiology. These were metabolite characterization, HLA and PGB analyses,

and exposure-response relationships. At this time no mechanism has been identified.

A special search category, or SSC, was established to ensure that adverse events represented the medical concept comprehensively, and that patients were counted once in the category. As you can see from the first row, there was a rash incidence of 34 percent in the peginterferon and ribavirin group. An additional 22 percent of patients experienced rash when telaprevir was added. The incidence of severe rash among Phase 3 telaprevir-treated patients was 3.7 percent. In Phase 3, the rate of discontinuation of all study drugs due to rash was low, at .8 percent.

This Kaplan-Meier here represents the pooled data from the placebo-controlled Phase 2 and 3 studies during the overall treatment phase of the studies. Time in weeks is on the X axis and proportion of patients on the Y axis. The orange line is telaprevir combination group, and the grey line is placebo with peginterferon and ribavirin.

You can observe that there was an earlier onset and higher incidence of rash when telaprevir was added.

Ninety-three percent of all rash events were mild or moderate, and the majority, more than 90 percent of rash events, did not progress to rash of greater severity. Rash resulted upon treatment completion or discontinuation. The majority of patients with rash received topical corticosteroids and/or systemic antihistamines. No data are available to assess the effectiveness of these treatments.

As you may be aware, in the literature rash is associated with PR and has often been characterized as an eczematous rash. As we saw before, in Phase 3 severe rash was reported in 3.7 percent of telaprevir-treated patients. The external adjudication panel reviewed all of these cases in addition to several others.

Severe rash was characterized as follows: primarily an eczematous, pruritic, spongiotic dermatitis that involved less than 30 percent of the body surface area. There was no evidence of

vasculitis or type 1 hypersensitivity reactions. Rare cases had features suggestive of severe skin reactions.

We will now move on to review the rare severe skin reactions observed across the development program.

To ensure a systemic adjudication, the scoring system from the European Registry of Severe Cutaneous Adverse Reactions was adapted. Importantly, in this scoring system, cases adjudicated as possible were not considered likely to be true cases. The external panel suspected Stevens-Johnson syndrome in three cases. All these cases resolved.

One of the three cases was assessed as a definite case. It occurred 11 weeks after the last dose of telaprevir, while the patient was still on peginterferon and ribavirin, as well as buproprion and naproxen. It was considered unrelated to telaprevir. Of the other two cases, one was assessed as probable and one as possible.

The panel also suspected drug reaction with

eosinophilia and systemic symptoms, also called DRESS, in 11 cases. Ten resolved. One was reported as resolving but was later lost to follow-up. One of the 11 cases was considered as a definite case. Of the remaining 10, 2 were considered as probable and the remaining 8 denoted as possible.

The predominate features across these cases were fever, rash, and eosinophilia. As you may appreciate, fever is also a common reaction to peginterferon. Systemic organ involvement, which is a hallmark of DRESS, was absent in 9 cases, and unconfirmed in 2.

In the Phase 3 program, rash management was included per protocol. Investigators were asked to follow general management principles, including monitoring for all rash events and symptomatic treatment as required. Guidance to distinguish three categories of rash was also included. These categories were: mild or moderate rash, severe rash, and among the severe rash, the category of rare severe skin reactions.

For mild and/or moderate rash, study drug discontinuations were not required. For severe rash, discontinuation of telaprevir was required. Telaprevir could not be reduced or restarted. Importantly, peg/ribavirin could be continued per clinical judgment. For rare severe skin reactions, which are also described with PR, permanent discontinuation of all study drugs and all medications was required.

As you will recall, in the Phase 3 program the rate of discontinuation of all study drugs due to rash was .8 percent. This was an improvement over the 5.2 percent that we had observed in the Phase 2 program, suggesting that the Phase 3 rash management plan here, shown here, was effective.

Next we will move on to a review of anemia. This here is a graphical representation of the pooled data from the placebo-controlled Phase 2 and 3 studies. Time in weeks is on the X axis, and the mean hemoglobin in grams per deciliter on the Y axis over the course of the studies.

The grey line represents placebo plus

peginterferon and ribavirin, which is associated with a decline in hemoglobin, as you can see. Now, the orange curve shows that when telaprevir is added, there was about an additional 1 to 1.5 gram per deciliter decrease in hemoglobin.

The vertical lines here are the relevant time points. The nadir in both groups was between weeks 12 to 14. In the telaprevir combination group, you can see that the mean hemoglobin returned to peginterferon and ribavirin levels after telaprevir was completed by about week 24. At the end of the study, the last vertical line, you can observe that there was no difference between the mean hemoglobins of the two groups.

This table compares the post-baseline hemoglobin nadirs between groups. 36.8 percent of patients in the telaprevir combination group had hemoglobin values less than 10 grams per deciliter compared with 14.8 percent of patients in the placebo plus peginterferon and ribavirin group.

In the telaprevir combination group, 27.3 percent of patients stayed between 10 and

8.5 grams per deciliter, and 9.5 percent were below 8.5 grams per deciliter. The comparative values for placebo plus peginterferon and ribavirin group were lower.

The potential mechanism of anemia has been evaluated. From a nonclinical perspective, repeat dose toxicity studies in rats and dogs suggested extravascular hemolysis as the mechanism. This was accompanied by a regenerative response. In vitro red blood cell mechanistic studies did not demonstrate a direct effect.

From a clinical perspective, the exposure-response analyses suggested a relationship between grade 2 or greater hemoglobin decline with telaprevir, peginterferon, and ribavirin exposures. The reticulocyte production index, or RPI, was obtained from the clinical studies. This analysis suggested that peripheral destruction of red blood cells as well as a lower red blood cell production both contributed to the observed anemia in telaprevir combination treatment.

This here is a summary table of the anemia

special search category adverse events. From the first row, we observe that 35.7 percent of patients in the telaprevir combination group reported an anemia adverse event compared with 16.6 percent in the placebo and peginterferon/ribavirin group.

Reviewing the last row, we see that rate of discontinuation of all study drugs for anemia was low at 1.3 percent in telaprevir-treated patients, compared with .4 percent in the placebo combination group. These are the comparative rates for ribavirin dose reduction in the two groups. The rates were higher in the telaprevir combination group.

In the Phase 3 program, management of anemia was included per protocol as follows: hemoglobin monitoring in accordance with the peginterferon and ribavirin labels, as well as clinical judgment; ribavirin dose modification per the ribavirin label; discontinuation of telaprevir, per clinical judgment, and telaprevir could not be reduced or restarted; and discontinuation of telaprevir was required any time that ribavirin was discontinued.

Blood transfusions were reported in 6 percent of telaprevir-treated patients and 1 percent of placebo/ peginterferon/ribavirin-treated patients.

In line with FDA guidance during the Phase 3 program, erythropoietin-simulating agents, or ESAs, were not permitted per protocol. They were used in 1 percent or less of patients across treatment groups. This has allowed for an unbiased assessment of anemia incidence as well as severity.

Next we will collectively review anorectal adverse events such as hemorrhoids, anorectal discomfort, and other similar events.

A special search category was established for a comprehensive evaluation. As you can observe from the summary table and the first row, these adverse events were frequent and reported at a higher incidence in the telaprevir combination group. However, these adverse events were rarely severe, with less than .5 percent of patients discontinuing for these events.

This brings us to the conclusions on telaprevir's safety profile. Telaprevir's safety

profile is based on exposure in more than 3,800 patients. Addition of telaprevir to peginterferon and ribavirin increased the incidence of specific adverse events. The majority occurred in the first 12 weeks, were mild to moderate, and did not lead to treatment discontinuation.

Rash and anemia were identified as key telaprevir-associated adverse events. Addition of telaprevir resulted in an increased incidence and severity of these events, as well as treatment discontinuations. Rash and anemia were well characterized during the development program, and both were reversible and manageable. Early recognition of these key events helped us characterize them and develop management strategies that were tested in Phase 3.

Thank you for your attention. I would now like to turn the podium back to Dr. Kauffman.

Sponsor Presentation – Robert Kauffman

DR. KAUFFMAN: Thank you, Dr. Singhal.

I'd now like to discuss the overall benefit-risk assessment of telaprevir.

Telaprevir represents a true paradigm shift in the treatment of HCV. Treatment with a telaprevir-based regimen resulted in significantly and markedly higher SVR rates compared to current treatment. This greater response was observed across genotype 1 treatment-naive and treatment-experienced populations, including relapsers, partial and null responders, and other groups that are traditionally considered poor responders to current treatment.

Null responders, those with the poorest response to peg and ribavirin, have only a 5 percent chance of SVR with current treatment; but with telaprevir, null responders have a substantially improved outcome. Although SVR rates were lower in absolute terms compared to other populations, substantial numbers of null responders can be cured with telaprevir.

In up to two-thirds of treatment-naive patients, these higher SVR rates can be achieved with 24 weeks of treatment, half the current treatment duration. Results from the clinical

development program also support response-guided therapy for patients with prior relapse. Overall, these significant benefits outweigh the risks of adding telaprevir to the current peginterferon/ribavirin treatment.

Illustrated here are the proposed treatment regimens. Response-guided therapy for treatment-naive and prior relapse patients will rely on HCV RNA evaluations at weeks 4 and 12, evaluations that are already in common use today. The regimen for null and partial responders is straightforward, at 48 weeks for all patients.

Most patients who do not achieve an SVR had telaprevir-resistant variants after treatment failure. These represent 12 to 22 percent of all patients starting treatment. Telaprevir-resistant variants show cross-resistance to other protease inhibitors but do not confer cross-resistance to direct-acting antivirals with different mechanisms of action; for example, polymerase or NS5A inhibitors.

Follow-up data indicates that resistant

variants decrease in frequency over time, including in null responders, who have the highest rate of virologic failure. We recognize the clinical significance of these findings have not been evaluated, but it's encouraging that in most patients, resistant variants diminish and in many cases are no longer detectable over time.

The data presented earlier by Dr. Singhal showed that the safety profile of telaprevir is well characterized and that adverse events are manageable. Rash and anemia are the most clinically significant adverse events associated with telaprevir.

Most cases of rash are mild to moderate and are primarily described as eczematous. Rash is reversible after treatment completion. Severe rash is manageable with early recognition and sequential drug discontinuation. Few patients stop all treatment due to rash. Instances of severe skin reactions were rare. They resolved with treatment discontinuation.

As you saw earlier, telaprevir produces an

incremental, approximately 1 gram per deciliter, decrease in hemoglobin that responds to ribavirin dose reductions and to ribavirin and telaprevir discontinuation, if necessary. Only a small proportion of patients discontinued treatment due to anemia. SVR is not compromised by ribavirin dose reduction. Adverse event management for rash and anemia have been implemented in Phase 3 and can be applied in practice with appropriate education.

Vertex is committed to providing information to treating physicians and patients on the risks associated with telaprevir and strategies for minimizing these risks. As we have described, the identified risks of telaprevir are rash and anemia. In addition, we plan to educate on other important topics, including the contraindications, warnings, and precautions outlined in the label; the importance of taking telaprevir with food, and adherence with the dosing regimen to minimize virologic failure; the need for precautions against pregnancy related to the teratogenic potential of ribavirin and potential reduction in the

effectiveness of oral contraceptives through a telaprevir-drug interaction; and the potential for other drug-drug interactions that may result in the need for alternative medications or dose changes during the 12-week period of telaprevir administration.

As we seek approval today for the proposed indication, we are also continuing to study the efficacy and safety of telaprevir in specific areas. Although we studied several hundred African American patients in our program, we plan to initiate a study later this year to expand our experience, particularly in those who have not responded to prior treatment and in patients with more advanced fibrosis.

We have an ongoing Phase 2 study in HIV/HCV coinfection. A phase 3 study will follow once the data are evaluated. Several HIV regimens are being evaluated for use with telaprevir in the current study.

We also plan to start a pilot study in post-transplant patients later this year. Hereto,

drug-drug interaction data with the commonly used immunosuppressive agents have been obtained. Studies in pre-transplant patients and patients with hepatic decompensation will be quite challenging. We are in discussions with experts in the field to evaluate the feasibility of an initial study in this population.

A pediatric dosage form is in development, and we plan a pediatric efficacy study for registration once this is available. And finally, we're also evaluating a twice-a-day telaprevir dosing regimen to provide better dosing convenience.

In conclusion, as you heard today, hepatitis C is a significant public health problem. There's an unmet need for treatment options that can increase SVR and reduce treatment burden. Telaprevir-based treatment results in significantly higher SVR rates compared to current treatment in patients with genotype 1 hepatitis C.

Telaprevir also reduces treatment duration for up to two-thirds of treatment-naive patients,

and response-guided therapy has also been shown to be appropriate for prior relapsers. The safety profile has been well characterized, and we have implemented practical management strategies for rash and anemia to protect patients.

The data presented today for telaprevir demonstrate that the benefits of telaprevir greatly outweigh the risks and represent a true advance in patient care. Thank you.

Clarifying Questions from Committee to Sponsor

DR. CARGILL: Thank you.

Clarifying questions from the committee for the sponsor? Dr. Clay?

DR. CLAY: Good morning. I want to commend Vertex on the array of drug-drug interaction studies they've already done as well as the ones they've planned. And in your ongoing and planned future studies, I saw on clintrials.gov that you also are doing one in people who failed telaprevir and continue in that study. So I want to commend you that that's already up there and listed.

But I want to focus in on some of your

safety issues. In the material provided by the Food and Drug Administration, they talk about your metabolite PZA, and they mention PZA is associated or a metabolite of niacin. But I'm more familiar with PZA as a metabolite of pyrazinamide, used in the treatment of tuberculosis.

You're describing a side effect profile that we expect to see from pyrazinamide. You've got increased uric acid, including incidences of gout. You have fever. You have anemia. You have thrombocytopenia. You have a rash. I'm not that familiar with the presentation of the rash in tuberculosis treatment.

But I guess this gets to the fact that you're giving single therapy to people, and I was curious if in your clinical trials, did you perform a PPD at baseline to see if someone was PPD-positive? And if so, had they already taken medicines for the treatment and prevention of tuberculosis?

DR. KAUFFMAN: We did not provide that information. We did not necessarily test patients.

It was really up to the clinicians who enrolled patients to decide if they were eligible for the trial. There was no specific inclusion or exclusion criteria related to prior tuberculosis status.

I'll point out, though, that the concentrations of pyrazinamide, although it is -- pyrazinoic acid, although it is a metabolite of telaprevir, are much lower than the concentrations that are present when pyrazinamide is used as a therapeutic agent.

DR. CLAY: I don't doubt that. But the side effect profile really looks like you're giving full-dose pyrazinamide. And I'm just curious how much information is provided to the investigators so that they could say, well, we need to test for TB in people before we give them this medicine.

I guess maybe it gets to -- I didn't have a great deal of information about how much of your drug ends up being pyrazinoic acid, and so maybe that would be helpful to me to know that.

DR. KAUFFMAN: Yes. I'll ask Dr. Garg to

come up and discuss that.

DR. GARG: Varun Garg, senior director of Clinical Pharmacology.

If I understand your question correctly, you're asking about how much of a dose difference or exposure difference is there between pyrazinamide and telaprevir. Is that correct?

DR. CLAY: No, not really. I don't really need to know how much of your drug ends up being pyrazinamide or pyrazinoic acid because it looks like there's a lot of pyrazinoic acid on board here.

I guess maybe if you could clarify for me -- you're broken down into three different metabolites, and so your major metabolite is this. So maybe go ahead and tell me, in relation to normally what we would expect with administering pyrazinamide, how much pyrazinoic acid made it to the patient's plasma.

DR. GARG: Right. So in the literature, the pyrazinoic acid concentrations that are described are about 14- to 150-fold higher when you

administer a single dose of pyrazinamide to healthy volunteers. There is very little data on pyrazinoic acid PK, but from the literature that we could obtain, the levels are anywhere from 14-fold higher to 150-fold higher, or more, with a single dose of pyrazinamide.

DR. CLAY: In your 24-hour urine collections, which I'm assuming you did, did you sample for 5-hydroxy?

DR. GARG: No. We actually did not measure pyrazinoic acid in the urine. We only did that in the plasma.

DR. CLAY: Thank you.

DR. CARGILL: Thank you. I have a question that relates to slide -- two questions. The first relates to slide CS-6, in which you indicate there were 64 patients in the telaprevir/peg/ribavirin group that were noncompliant compared to 9 in the placebo group. And I guess my questions are, of those who were nonadherent, what were their characteristics?

My second is, you also indicate in the

presentation decreased evidence for reduced oral contraceptive effectiveness. And so I would like to know if female patients taking these medications were counseled to use an alternate form of birth control.

DR. KAUFFMAN: So with respect to your second question, yes, they were. We recommended an additional barrier method of contraception during the period of telaprevir administration and for two months after. These patients did not necessarily have to stop their oral contraceptive, but obviously we could not rely on it for effectiveness, so additional barrier methods were recommended in the protocols.

DR. CARGILL: And with respect to the first question about the 64 patients who were noncompliant?

DR. KAUFFMAN: Yes. I don't have information on the characteristics of those patients. We measured adherence through various methods, and, yes, there was some during the telaprevir dosing period.

DR. CARGILL: Ms. Dee?

MS. DEE: You know, I noticed in the briefing document that you supplied to us that 50 percent -- I mean -- yes, the investigators thought that there was a rash over 50 percent of the body surface area, and once the DEP was in place, that they characterized it as 30 percent.

It would seem to me that it would be easy to look and decide between whether it's 30 or 50 percent of a rash on a body surface.

Why did it go down 20 percent once the DEP reviewed it?

DR. KAUFFMAN: Yes. When the DEP reviewed these cases, they consider the intervening skin around areas of rash to be not included in the body surface area; whereas when the investigators looked at patients, they kind of estimated the body surface area by what they thought was the amount of rash that covered the skin, and they estimated it higher. The DEP, when they looked at it, they re-estimated the amount of body surface area and downgraded it for that reason. You know, if you

have a patch of rash in a certain area, the investigators likely counted it as encompassing that whole area, whereas the DEP looked at the amount of intervening skin and made an estimate of the actual coverage of the skin surface area. So there was a difference.

DR. CARGILL: Thank you.

Dr. Ghany?

DR. GHANY: Yes. In your Phase 3 trial where you compared T8 to T12 dosing, it was primarily to limit exposure to telaprevir. Could you tell us if there was a difference in the incidence of rash between those two arms? And if so, then I'd like you to answer a second question for me. Perhaps if you could explain what accounts for the difference in SVR rates between the T12 and T8 groups. I think the delta was 7 percent, but they had similar rates of early rapid virological response as well as similar relapse rates.

So was it due to higher on-treatment response rates in the T12 group, or was it due to a higher rate of resistance?

DR. KAUFFMAN: Yes. So let me just give a little background.

The hypothesis behind the 8-week telaprevir duration was based on observations in Phase 2, where it appeared that there was a higher incidence of severe rash occurring in the third month of therapy, from weeks 8 to 12. Therefore, we decided to evaluate a shorter duration of telaprevir.

We chose 8 weeks because all of our modeling and Phase 2 data suggested that we would not likely give up very much antiviral efficacy with 8 weeks of telaprevir. And that, of course, was the hypothesis that was tested.

In the outcome of the study, it's true there was a small difference in the rate of severe rash, with about an absolute 2.5 percent lower rate of rash in the 8-week arm compared to the 12-week arm. But as you point out, there's a difference in the SVR rates, and that's largely accounted for by a somewhat higher rate of our breakthrough or virologic failure in the 8-week arm.

So the 8-week arm has a little less

virologic activity, if you will, and in a sense, that's the tradeoff for a very small difference in the occurrence of severe rash.

DR. CARGILL: Thank you.

Dr. Connick?

DR. CONNICK: I wanted to ask a few questions about CE-14 and CE-31 relating to evidence supporting efficacy in subpopulations. I guess I want to say it's disappointing that your recruitment of blacks was so low, given the significant amount of disease in that population in this country.

Let's see. On CE-31, I believe, the data are not -- the confidence interval crosses 1 for blacks. So I wanted to ask, do you have data from other studies that you can combine to convince us that in the treatment-experienced African Americans that there is efficacy?

DR. KAUFFMAN: So as you point out, in large part because of the geographic distribution of the patients that were enrolled in study C216, with relatively fewer coming from North America, the

inclusion of black and African American subjects was reduced in that population.

We have enrolled African Americans in other Phase 2 studies in treatment-experienced patients, and their outcomes are really quite good, although, as has been true throughout the program, overall SVR rates in African American patients are lower than for Caucasians. Even though there's still a great incremental gain with telaprevir, nevertheless the absolute levels are still lower.

But we have, yes, only a limited experience in the treatment-experienced population. But that was a reason for us considering an additional study that we are going to start later this year to try to expand our experience in that population, particularly in the treatment failure population among African Americans.

DR. CONNICK: So I noted also on both of those slides, CE-14 and 31, that people over 65 again didn't -- the confidence interval crossed zero. Do you feel that there may not be benefit in treating older individuals, or was this because

that was such a small number?

DR. KAUFFMAN: Our view, obviously, is that the overall efficacy is very high with telaprevir. There's certainly no reason to think, a priori, that there would be any issue in those who are over age 65; that, as you point out, the confidence interval is quite broad because there were only small numbers of patients in that age range that were included.

DR. CONNICK: Thank you.

DR. CARGILL: Thank you.

Ms. Valbh?

MS. VALBH: Hi. I have a couple of questions. My first question is a follow up on Dr. Cargill's question about compliance. How did you assess compliance in these patients? What tools were used to assess compliance?

Then my other question is, even though a small percentage of patients used EPO in your trial -- I think it was 14 patients -- at what point was the EPO initiated? So what was the hemoglobin level? And then also, if you can

comment on, in the anemic patients, after telaprevir was discontinued, comment on the hemoglobin levels and how quickly they came back.

DR. KAUFFMAN: Yes. There are several questions there. Maybe I can start with the first one on adherence.

We estimated adherence based on pill counts, on drug accountability records, and on the start and the stop dates in the CRF. And in addition, patients filled out diaries about when they took their medications. Adherence overall was really very good. More than 95 percent of patients took more than 95 percent of their drug.

Remember, the telaprevir dosing period is only 12 weeks, and therefore patients can be coached through that and can be coached on the importance of taking their medication as prescribed.

Sorry. Can you remind me now of the other questions?

MS. VALBH: Sure. On the 14 patients that were placed on EPO, what was the hemoglobin value

when EPO was initiated?

DR. KAUFFMAN: I'll ask Dr. Singhal to come up and address that question.

DR. SINGHAL: So EPO was used in a small number of patients, and I'd like to just go back to the initial point that it wasn't permitted. Now, there was a special permission given for the C216 study, which was the REALIZE study, in France at the request of the study -- of the AFSSAPS. And so they were allowed to use EPO, and that was really where most of the EPO was used.

So it wasn't really used in North America for the Phase 3 program. I don't have the exact levels, but it seemed to be based more on a practice rather than on a hemoglobin level.

MS. VALBH: On a practice.

DR. SINGHAL: And with regards to your question about hemoglobin recovery, I'd like to point out also on the curves that, as we demonstrated earlier, the hemoglobin rises up as soon as telaprevir is discontinued to peginterferon and ribavirin levels, and then gradually rises up

to peginterferon/ribavirin levels over the following 12 weeks after telaprevir is completed, so by 24 weeks. And the most significant rise is after peginterferon and ribavirin are pulled off and completed.

MS. VALBH: Okay. And, I'm sorry, I have one more question. On one of the slides there was a mention that there was guidance on symptomatic management of rash. Can you tell me a little bit about what that guidance was? Did you have an algorithm that, if a rash presented itself, start with a topic corticosteroid, or you start with an antihistamine? What was that guidance?

DR. KAUFFMAN: Yes. I'll ask Dr. Singhal to come up and tell you about that.

DR. SINGHAL: A very specific guidance was included in all the Phase 3 protocols, and let me begin by the general principles that were included.

So the general principles were that physicians needed to follow the general management principles and use systemic antihistamines as required for pruritus or rash, as well as topical

corticosteroids. There was a specific mention that if they needed to use topical corticosteroids for more than two weeks, they needed to connect with a medical monitor to allow whether it was going to be systemically absorbed.

Very specifically, systemic corticosteroids were to be used only as indicated and if required when other modalities had failed because systemic corticosteroids, once they were used, we required telaprevir and other drugs to be discontinued. So that was the specific management.

Now, this was a general principle management across all grades of rash. So I just want to go back to the management that I provided. This was the general management as well as the symptomatic treatment. We do have the details of how many patients used these treatments, and if you like, I can share that with you.

With regards to study action, it was really very clear. Mild and moderate rash did not require any discontinuation, and that was more than 93 percent, as we saw. And then the severe rash

required discontinuation of telaprevir alone.

MS. VALBH: Thank you.

DR. CARGILL: Thank you.

Dr. Bigby?

DR. BIGBY: I think that there's a great deal of unclarity about the definitions of the words that you're using, so I have several questions in that regard. I think probably Dr. Singhal would be the one to address these.

You used the term "severe rash," and then in that slide at CS-16 at the bottom, you have "severe skin reaction." So could you just tell us what is your definition of severe rash?

DR. KAUFFMAN: Yes. I'll ask Dr. Singhal to come up.

DR. SINGHAL: For the Phase 3 program and the Phase 2 program, this definition was very specifically included in the protocol. Severe rash was defined as any rash which, per the investigator -- and maybe I can have SC-10, please; thank you -- which would -- the grade 1 rash was a localized eruption. A grade 2 rash was a diffuse

eruption which maybe occupied less than 50 percent of the body surface area.

Then as you see here, the grade 3 rash really encompassed two concepts. The first one was a generalized rash that occupied more than 50 percent of the body surface area. But it also included a rash that may indicate a severe skin reaction. So I'll stop here for a moment.

The severe skin reactions, which is the second sub-bullet under the last bullet here, would be constituting a potentially life-threatening skin reaction which would be also possibly attributed to drug, such as Stevens-Johnson syndrome. And we wanted to make sure that the management for these two different types of rash was different.

The first, generalized severe rash that did not have any of the features listed here, required only telaprevir to be discontinued. But if there was any suggestion of bullae, vesicles, mucous membrane involvement, target lesions, or others, it required all study drugs to be discontinued. And that was the distinguishing feature between the

severe skin reaction and the severe rash.

DR. BIGBY: That's clear. Okay. And the second part of the question is, did you have any cases of TEN?

DR. KAUFFMAN: I'm sorry. I didn't hear that last part.

DR. BIGBY: Did you have any cases of toxic epidermal necrolysis?

DR. KAUFFMAN: No, we did not.

DR. CARGILL: Thank you.

Dr. McGovern?

DR. MCGOVERN: I just have a couple of quick questions. The first one is just administration. You might have even mentioned this, but I might have missed it.

I think your drug is two tablets per dosing interval. I just would like clarification of that. Also, if you can give us some guidance on what you described as food with the pills.

A third one is related to resistance. You showed us a slide that shows the disappearance of RAVs much faster with genotype 1B patients.

Do you have any information about the various RAVs between genotype 1Bs and 1A patients, whether the disappearance is related to viral fitness. And also, do you have any information on -- in the lead-in phase of C216, do you have information on whether there was any benefit in terms of the lead-in in terms of the formation of RAVs?

DR. KAUFFMAN: Yes. I'll take the first part, and then I'll ask Dr. Kieffer to come up and discuss the resistance issue.

You were right. The dosing was with two tablets taken three times a day. The recommendation for food was that telaprevir be taken with a normal meal or with a snack, and it was asked that the snack contain some fat. It didn't have to be a lot of fat, but some fat. But otherwise, a normal meal is what was recommended.

Now Dr. Kieffer to answer the remaining questions.

DR. KIEFFER: So, as you mentioned, we did observe a difference in the evolution of resistant

variants during follow-up between subtype 1A and 1B.

If I could have VR-52, please? And so the reason for that is that we do observe different variants between subtypes. So what this slide shows you is the type of variants we observed between subtype 1A and 1B. So the majority of resistant variants observed in subtype 1A include V36M, R155K, and the double variant V36M and R155K.

In subtype 1B, those patients mostly have V36A, T54A, and A156S or T. And we believe that there's likely a fitness difference in these variants, and that is what causing the observed difference in the decline of the resistance over time in the absence of treatment.

To your last question about differences in resistant mutations in the lead-in versus no lead-in, if I could show VR-56. This slide will show you the different types of treatment failure and whether or not patients had detectable resistance. The wild type is in green; these are patients that did not have any detectable resistant variants by

population sequencing. And then orange indicates patients where telaprevir-resistant variants were detectable. And you can see that there's really no difference between the arm with a lead-in or without a lead-in for all categories of response.

DR. CARGILL: Thank you.

Dr. Murata?

DR. MURATA: Thank you. I have questions on anemia management, if there was a brief -- regarding slide 26 of the safety section -- if the guidance on hemoglobin monitoring can be briefly reviewed.

With respect to the blood transfusions, in addition to the percentages that you've shown, if you can provide additional details; for example, number of red blood cell units transfused per patient or how many transfusions were permitted prior to drug discontinuation.

DR. KAUFFMAN: Yes. I'll ask Dr. Singhal to come up to address that.

DR. SINGHAL: Please, may I ask you to repeat your question? I'm not sure I followed it.

DR. MURATA: So the question is in two parts. One, if you can briefly provide an overview, as you did for the rash, but instead for the hemoglobin monitoring. Second, if you can provide additional information or clarification of the blood transfusions that were permitted and occurred during the study; specifically, the number of transfusions that were permitted prior to drug discontinuation, and on average, for those who required transfusions, how many transfusion events did occur.

DR. SINGHAL: So with regard to the transfusion, there wasn't any specific guidance within the protocols that linked transfusion to discontinuation. However, there was guidance to follow the ribavirin label.

So, in general, investigators did follow the guidance, and the guidance was that if it was less than 10 grams per deciliter, then investigators had to reduce ribavirin -- had to follow ribavirin dose modification; and if it was less than 8.5, they needed to discontinue. And whenever they

discontinued ribavirin, we did have a rule in place that they needed to discontinue telaprevir.

So, in general, that was the guidance that we provided. Transfusions were used in 6 percent of the patients across the Phase 3 program, and I don't have specific values. These were also -- some of these were based on local practice. And so there wasn't necessarily a trend across the level at which they were used.

DR. CARGILL: Thank you.

Dr. Strader?

DR. STRADER: I'd just like to follow up on that point you just made. Were there any patients who had anemia occur after the 12 weeks of telaprevir was given? And if so -- obviously, if you're discontinuing the ribavirin, the telaprevir dose is already finished -- do you treat those patients with peginterferon alone or is the dose discontinued, both medications discontinued at that point?

DR. KAUFFMAN: Dr. Singhal?

DR. SINGHAL: So if I understand your

question correctly, did anemia occur after telaprevir was discontinued? Yes, there were some cases of anemia that were reported after telaprevir was discontinued. I just want to remind you that the way that the calculation and the displays are done, we pick up the worst and the most severe event of anemia, and these tended to occur in the first 12 weeks.

So although patients may have experienced an event later on, you wouldn't necessarily see it on that display. And after that, if they had discontinued telaprevir and ribavirin, they could continue through the study on peginterferon, and of course if they had to stop that because the anemia continued. But those were fewer instances, very few.

DR. STRADER: Two more quick questions. One of them, there's a slide CS-17 where you're showing the rash with telaprevir and with placebo. And it appears that you indicate that the rash continues even though the telaprevir dose is discontinued, and for a long period of time.

But I was under the impression that once the telaprevir dose was discontinued, the rash resolved. So can you just clarify that slide for me, please?

DR. KAUFFMAN: Yes. Dr. Singhal?

DR. SINGHAL: Yes. I can clarify that. The point here was that, in general, we have noted that there is a background rate of rash, mild and moderate rash, with peginterferon and ribavirin, to the rate of about 34 percent. When we added telaprevir to that regimen, there was an increase in the rate of mild and moderate rash. And then there was a severe rash that wasn't really noted at all in the placebo/peginterferon/ribavirin group. It was only noted in the telaprevir groups, as we demonstrated.

So when telaprevir was discontinued by the rules that we had established, remember, the patients were still on peginterferon and ribavirin, so they had the underlying peginterferon and ribavirin. We believe that that may be contributing to an increased time to resolution.

In general, the severe rash could take about 4 to 6 weeks to resolve completely. That was the median time to resolution, which is why I wanted to make the point that it doesn't go away immediately.

DR. STRADER: Okay. One last question. The treatment of treatment-experienced patients, you chose for some reason not to use response-guided therapy in those groups. Is it because you had done some Phase 2 studies that you don't show us here that show that there was a response in response-guided treatment? Why was it that you decided not to do response-guided therapy for treatment-experienced patients?

DR. KAUFFMAN: When we designed the C216 study, some of those data were not available, and we chose the conservative route of treating patients for the full duration, given that they had already failed treatment. Also, there's only so many questions one can usually ask in a clinical trial, and therefore we decided to keep it simple and just used 48-week treatment for all patients.

DR. CARGILL: Dr. Van Dyke?

DR. VAN DYKE: Yes. I had one question about viral resistance. You mentioned that there was cross-resistance with other protease inhibitors. Does the drug have any activity against HIV, and is there potential for developing protease inhibitor resistance against HIV protease inhibitor drugs?

DR. KAUFFMAN: Yes. We actually have examined that in vitro, and there is no cross-resistance with HIV. There's no effect on HIV.

DR. VAN DYKE: Great. Super. My other question is, could you give us more clinical details on the anorectal symptoms in terms of what they were, what did they look like clinically, and how long did they last, and how much of a problem really were they for the subjects? Because they were quite common, like 29 percent.

DR. KAUFFMAN: Yes. We first became aware of this in Phase 2 with increased reports of hemorrhoids. And, frankly, I don't think it was really hemorrhoids, but hemorrhoids are present very commonly, so when you take a look, you often

will find hemorrhoids, even if they're not really related to the phenomenon.

We have really only anecdotal reports. But I have spoken to many investigators about this phenomenon. Upon examination, there is no inflammation. Either externally or on anoscopy, there's been no inflammation. And I'll just point out parenthetically that in all of our nonclinical studies, there is no inflammation or other findings related to the colon with telaprevir.

It's described as a burning sensation or an itching sensation. It occurs relatively rapidly after the beginning of administration of telaprevir. It actually often resolves either during the period of dosing or very rapidly thereafter. And as we pointed out, it's almost never associated with treatment discontinuation. It is an annoying side effect, but it really doesn't have any serious consequences in terms of compliance with the treatment regimen.

DR. CARGILL: Thank you.

Dr. Knodell?

DR. KNODELL: I'm just trying to get a global feel for how often you have to discontinue this treatment. And I'm looking at slides C-6 and C-10. And before I ask the question, I assume that in your response rates, everybody who got telaprevir, even if they only got a couple doses and discontinued treatment, is included in your analysis?

DR. KAUFFMAN: That's absolutely correct. It was intent to treat, and everyone who started treatment was accounted for at the end.

DR. KNODELL: Your response rate for people who actually complete treatment is really quite a bit better than what you list.

My question is, it looks like that you have, overall, fairly severe adverse events in about 16 percent of your telaprevir group versus 7 percent overall in your dual therapy, and that your discontinuation rate, if you look at all discontinue rates that aren't for viral failure, is about 20 percent versus 10 percent.

Going forward, is that what we can expect,

that probably about 20 percent of patients aren't going to be able to make it through this treatment regimen?

DR. KAUFFMAN: Obviously, I can't speculate on what will happen in the future. We can only say what we saw in the trials. But yes, there are an increased rate of discontinuations due to telaprevir compared to the control treatment. This is due to a number of causes, but obviously, as we've pointed out, most prominently due to anemia and to rash.

DR. CARGILL: Thank you.

Dr. Korman?

DR. KORMAN: I wanted to ask a question about the side effect profile. You pooled the data for the treatment-experienced and treatment-naive patients, I think; that's all that I saw. I'd be interested in knowing whether the treatment-experienced patients that have more advanced liver disease have a different side effect profile and whether the rash can be predicted by treatment-experienced patients having had skin reactions of

either mild, moderate, or severe characteristics.

At least in my experience, many of the patients, particularly the female patients, complain of hair loss, and I notice that that's not included. I wondered if that actually is also something that other hepatologists see, and whether you can comment on seeing that during this process. It's clearly a very disturbing symptom.

DR. KAUFFMAN: Yes. Just overall, the adverse event profile in the treatment-experienced patients was very similar to the treatment-naive patients, and that's why we were able to pool those groups together.

I'll ask Dr. Singhal to come up and address your other questions in more detail.

DR. SINGHAL: So I'll just address, actually, your second question first about the hair loss.

DR. KORMAN: Complicated.

DR. SINGHAL: Okay. No, I just wanted to mention that the alopecia, which is actually commonly noted with peginterferon and ribavirin, we

did not see any increased rates with telaprevir at all, which is why it was not mentioned as part of -- and it's below 20 percent, so it didn't make it to the most common AEs, either. So that's for --

DR. KORMAN: The second question.

DR. SINGHAL: -- the second question. And the first question is that the treatment failure and the treatment-naive patients actually looked very similar in their safety profiles. There were a few events that seemed to occur at a higher incidence in the treatment-naive population, and these are primarily nausea and vomiting. With the rash as well as the anemia, we did not find any notable differences.

DR. KORMAN: Just quickly, about photosensitization, did you make any recommendations?

DR. SINGHAL: Right. So we did examine that from a nonclinical perspective, the photosensitization, and we do not believe that it contributes to the rash in any great way. From a

clinical perspective, the dermatology expert panel also examined this based on about 150 cases with photographs that they examined, and there did not seem to be any indication of it being photosensitive.

DR. CARGILL: We will now take a 15-minute break. For those committee members who still have outstanding questions, we will return to those questions.

Panel members, please remember that there should be no discussion of the meeting topic during the break among yourselves or with any member of the audience. We will resume promptly at 10:30.

(Whereupon, a recess was taken.)

DR. CARGILL: We're going to resume the meeting, if you could please take your seats.

I'm going to take the chair's prerogative, as there have been a number of questions around rash and the side effect, and ask the sponsor to please show us the slides of the rash before we proceed with the FDA presentation.

DR. KAUFFMAN: Thank you. It's coming up

now.

Can we put the slide up?

DR. CARGILL: Thank you.

DR. KAUFFMAN: It's a little difficult to see. It's a little dark on the screen.

DR. CARGILL: We're going to ask for the lights to be dimmed, if you can give us one moment, so this can be seen very well.

DR. KAUFFMAN: Sure.

MR. TRAN: We are asking the staff to dim the lights for us. Thank you. Hang on for a moment.

[Pause.]

DR. CARGILL: Now that we actually have seen this rash, I'd like to just ask the committee members if they have any specific questions after seeing this, to please address them now so we can go on to the next presentation.

DR. KAUFFMAN: If you like, I can go through the slide. It's just not quite so visible.

DR. CARGILL: Why don't we let the sponsor go through the slide, and then if you would follow

up with your question.

DR. BIGBY: Sorry?

DR. CARGILL: I said we're going to let the sponsor go through his slide, and then have you follow up with your question. Thank you.

DR. KAUFFMAN: Fine. So this slide shows a series of photographs of a rash that's been associated with telaprevir.

I'll make a couple of general points. One is that -- if I can use the word "typical," and I use it advisedly -- the typical telaprevir rash is as described. It's a primarily eczematous eruption. And the difference between mild, moderate, and severe is related primarily to the amount of skin area that's involved. The rash itself morphologically is the same; it's just the amount of skin involvement.

As we noted, the vast majority of rashes are mild and moderate, 93 percent, and those are shown in the two panels on the left: mild, which is described as localized, as we pointed out, and moderate, which is present on less than 50 percent

of the body surface area.

It's a little difficult to see, but the severe rash, which occurs on more than 50 percent of the body surface area, represents only about 6 and a half percent of all rash events. And there's a closeup of that rash that shows you the amount of skin that's involved and the eczematous appearance.

DR. CARGILL: Thank you.

Dr. Bigby?

DR. BIGBY: I think it would be informative to the panel if you could also, if you have it available, just show an example of a case that was described as a potential SJS case, and also show the panel what a patient that has DRESS looks like.

DR. KAUFFMAN: I'm told we don't have slides available of either of those two available to show today.

DR. CARGILL: All right. Thank you.

We will now proceed with our presentation from the FDA. I would like to remind public observers at this meeting that while this meeting

is open for public observation, public attendees may not participate except at the specific request of the panel.

FDA Presentation – Russell Fleischer

MR. FLEISCHER: Good morning. On behalf of my colleagues on the telaprevir review team, it's a privilege to present the FDA's perspective on the telaprevir NDA.

Our presentation will focus on efficacy issues and safety issues. We're going to review some issues related to the Phase 3 trial design. Dr. Jadhav will come up and talk about some pharmacometric analyses on the response-guided therapy for prior relapsers. Then I'll come back and talk about virology, IL28B, and discuss a few interesting and important subgroups. I'll switch to safety, talk about rash, anemia, a little bit on the anorectal disorders, cover some clinical adverse events and some laboratory abnormalities.

So you've seen the trial designs from the sponsor, and you've seen the overall efficacy results. But each trial was actually designed to

answer an additional question. So in the study 108, the T8 arm was included to test if a shorter duration of treatment might change the risk-benefit assessment by improving tolerability, particularly by reducing the frequency of severe rash while not sacrificing efficacy.

In study 111, a 24-week regimen of peg and ribavirin versus 48 weeks was included to see if there was an increased efficacy associated with longer duration therapy for subjects who achieved an early response. And there was a delayed versus immediate start in study 216 to assess the effect of a short course of treatment with peg and ribavirin on the frequency of emergence of resistant strains during telaprevir exposure and to determine whether this strategy had an overall impact on efficacy.

So on study 108 -- you've seen some of this data -- about 58 percent of subjects in the T8 and T12 arms achieved eRVR, which was undetectable HCV RNA, at weeks 4 and 12. The SVR rates for the two regimens were 87 percent for the T8 group and

92 percent for the T12 group, which was about a 5 percent improved SVR rate. The difference was numerically higher but not statistically significant, and on a formal test for noninferiority, the 8-week duration would have failed to meet our overall standard for clinical equivalence.

In further looking at the advantages for the T12 compared to T8, as I just showed you, the SVR rate in early responders was higher at 92 versus 87 percent. For subjects who had no EVR and received 48 weeks of peg and ribavirin, the SVR rates were 62 percent for the T12 group, 55 percent for the T8.

The breakthrough rate on peg and ribavirin after telaprevir was completed was lower in the T12 group at 10 percent, compared to 16 percent. And I'll show you a little bit later that there was a suggestion for increased responses for CT and TT genotypes with the T12 regimen. We hypothesize that the extra 4 weeks of telaprevir suppressed potential substitutions that confer resistance to

telaprevir. Disadvantages, which you heard a little bit, was that there were additional cases of rash and anemia between treatment weeks 8 and 12.

In study 111, all 540 subjects started on telaprevir and peg/ribavirin for 12 weeks. Of those, 60 percent, or about 322, achieved an eRVR and were randomized to 162 to 24 weeks and 160 to 48 weeks of peg and ribavirin. You can see from the table the SVR rates were pretty comparable at about 90 percent.

For subjects who did not achieve an eRVR and received 48 weeks of peg and ribavirin, the SVR rate was 66 percent, which was again generally comparable to what was seen for the same population in study 108.

In study C216, studies were randomized to either an immediate start or, as the applicant said, a lead-in. We use the term "delayed start." It's the same thing, 4 weeks of peg and ribavirin, and then initiation of peg and ribavirin -- I'm sorry, 4 weeks of peg and ribavirin, and then telaprevir was added.

You can see that for all subjects, the SVR rates were comparable. Same for prior nulls. Prior partial relapsers -- I'm sorry. Prior partial responders and prior relapsers all were pretty comparable to each other, and when we further investigated, looking for differences, we didn't find any between the SVR rates for the delayed start compared to the immediate start for any nonresponse group or by any demographic or disease covariates.

So I'm going to turn it over to Dr. Jadhav to talk about his analysis of RGT in treatment-experienced prior relapse subjects.

FDA Presentation – Pravin Jadhav

DR. JADHAV: Thank you, Dr. Fleischer.

Good morning, everyone.

For my part of FDA presentation, I have one key question: Is response-guided therapy for prior relapse subjects acceptable? Why are we asking this question? Dr. Fleischer, as well as the sponsor, shared with you that the response rate in treatment-naive subjects who achieve eRVR was

greater than 90 percent whether peg/ribavirin was given for 24 weeks or 48 weeks.

Therefore, study 111 provides us a direct within-trial comparison to recommend 24 weeks of peg/ribavirin for all treatment-naive subjects who achieve eRVR. However, to recommend a 24-week duration of peg/ribavirin for prior relapse subjects who achieved eRVR, we have evidence from cross-trial comparison.

What I'm going to show you in the course of this presentation, that we can not only use data from cross-trial comparison to support 24 weeks of peg/ribavirin duration for this population, we can also use data from naive subjects to inform us about durations in prior relapse subjects. Also, viral dynamic modeling that sponsor has done, and I'm not going to present -- guide us in the same direction.

For the first evidence, we look at three studies, study 106, 107, and C216, as it has been presented before. C216 was the Phase 3 study, and 106 and 107 were the two Phase 2 studies.

These are the same data that sponsor has showed earlier, and in these studies, the prior relapse subjects were treated. So starting with the first bar in this plot, we observed greater than 90 percent SVR with 24 weeks of peg/ribavirin in prior relapse subjects who achieve eRVR. Similarly, the second and third bar shows that even with 48 weeks of peg/ribavirin in patients who achieved eRVR, the response rate was greater than 90 percent.

The point I would like you to take from the slide is that the response rate for prior relapse subjects with eRVR was greater than 90 percent, suggesting that 48 weeks of peg/ribavirin does not provide additional benefit on SVR.

Remember, the SVR rate for treatment-naive subjects overall with eRVR was also 90 percent, as sponsor has presented, for the same treatments, 24 weeks or 48 weeks. And please note that in all these treatment arms, telaprevir was given for 12 weeks.

So for those of you who believe these cross-

trial comparisons and similar evidence from naive, you can ignore rest of my talk.

[Laughter.]

DR. JADHAV: But if you don't, if you believe this is a cross-trial comparison, I would like you to provide second set of argument why we can support 24 weeks of peg/ribavirin for prior relapse subjects who achieved eRVR.

From this evidence, I'm going to take you to treatment-naive data. So before I show any data, let me first introduce, or in fact one more time try to introduce, a concept that we need to carefully think about, treatment-naive and -experienced subjects in context of peg/ribavirin.

Let's start with the treatment-naive subject. And when the subject is going through the first round of therapy, there are four possible outcomes. The subject might end up to be a responder, relapser, partial, or null. The treatment failures here are now called treatment-experienced, and to be very specific, these should be called peg/ribavirin-experienced.

In HIV subjects, if this was HIV treatment, these experienced patients also means they're resistants, and they would fail under retreatment. What we are able to see from this program, as well as the program that we reviewed yesterday, that if these subjects go through the second round of treatment, the response to peg/ribavirin is not lost.

What I'm going to show you here is data from study 108, where the treatment-naive patients who eventually ended up to be relapsers, what happened to them at week 4, we knew the response status in study 216 at the baseline, what happened to them at C216.

So for the terminology, what I'm going to call the patient on the left-hand side to be a future relapser because at week 4 I did not know the end-of-study status. For the patient on the right side, the patient will be prior relapser because we know the status. We find that the response at week 4 for the first -- that's the first row in this table, where it's a future

relapser -- is the same compared to week 4 response to peg/ribavirin for a prior relapse patient.

So what I'm trying to show you here is whether the relapse status was known or unknown, peg/ribavirin response is not lost; it's still the same. What I'm not saying here is that week 4 response can tell you who the relapser is. That is not the point, that the patient responsiveness stays the same on the first and the second round of treatment.

So for those of you who treat patients, think about it this way. Should the treatment approach be different, if the responsiveness PR is the same, but only that you know that they failed on the peg/ribavirin before, the point is the peg/ribavirin response is same even for these two patients.

The point I am trying to make, as I've been repeatedly saying, the patient's responsiveness to peg/ribavirin is not lost in peg/ribavirin failures. Therefore, whether it's a known relapser or a future relapser, a patient should be treated

in a similar way.

So if you agree with that principle, let me take you to treatment-naive data and let's understand, going through the treatment-naive population.

Here is the distribution of end-of-study outcomes for peg/ribavirin, the control arm only in treatment-naive, treated for 48 weeks of peg/ribavirin. We found 44 percent were responders, 18 percent relapsers, 19 percent partial responders, and 9 percent were nonresponders. So at the outset, our treatment-naive population is this mixed bag of future relapsers, future partial responders, future nulls, and obviously, the responders.

Because peg/ribavirin and telaprevir treatments were randomized, this distribution must be present in the telaprevir-treated group. So in telaprevir-treated group, when we find 79 percent of responders to triple therapy of which 54 percent had SVR and eRVR and 25 percent had SVR without eRVR -- so just to clarify, that 54 percent number

comes from 58 percent achieving eRVR, and of them, 92 percent achieving SVR. So if you take both combined, it's about 54 percent.

Now, you've got to stay with me on this.

[Laughter.]

DR. JADHAV: If you think about responders, 44 percent who are responders -- and hepatologists can help me with this. If you are a responder to a dual, which is the left-hand side, you are most likely to be a responder for triple. Correct? Makes sense. Once you are a responder for dual, you're a responder for triple. So we accounted for 44 percent in the right pie chart.

Let's think about who are these additional 10 percent who are achieving eRVR and SVR in overall population. Who is the most next likely group who we are going to give 24 weeks of peg/ribavirin because we studied them in treatment-naive population? Remember, the entire treatment-naive population is going to get 50 percent of them, SVR and eRVR, ending up to be the 24 weeks of duration.

So who are these patients? Most likely they are the relapsers, your future relapsers. So the point I'm trying to make is the most likely group is the future relapsers. So if you are treating a future relapser without knowing who they are, should you not be treating a prior relapser because their treatment response is the same, with shorter duration of peg/ribavirin?

Therefore, the 90 percent response rate you see in the EVR subjects from treatment-naive population, as realized from the relapser, is no artifact. In fact, I would credit sponsors one of the statements in their slide, it is not that the treatment-naive population and the relapsers are presented at 90 percent high interferon responsiveness, it's the patients with eRVR -- that's more important, the response to the current therapy -- are the ones that represent population with high interferon/ribavirin response, and the baseline status is less important than how you're responding to the current treatment than the previous.

Again, if you're interested, I can show you. Simple mathematics can explain why both numbers turn out to be 90 percent. It's no artifact.

So the point I'm trying to make is we can reasonably say that prior relapse subjects with eRVR can achieve SVR with 24 weeks of peg/ribavirin, about 90 percent of them. We have learned that the first and the second round of peg/ribavirin treatment does not make patients lose their responsiveness to peg/ribavirin. If that is so, the eRVR on the new treatment is more important than what happened to them in their previous round of therapy. Combined, these arguments support that prior relapse subjects can be treated with 24 weeks of peg/ribavirin therapy, given the 90 percent SVR from cross-trial comparison.

Thank you, and Dr. Fleischer will present other analysis from FDA.

FDA Presentation – Russell Fleischer

MR. FLEISCHER: Okay. So I'm going to give you some virology.

We found that almost all of the subjects who

did not achieve an SVR and who failed on telaprevir before week 12 had a treatment-emergent telaprevir-resistant substitution, and the majority of subjects who did not achieve an SVR and failed on peg and ribavirin after week 12 or who relapsed also had treatment-emergent telaprevir-resistant substitutions. And, overall, more treatment failures were in subtype 1A subjects.

So here are the treatment-emergent substitutions. We examined the data for these substitutions that emerged on telaprevir, and these are in subjects who did not achieve an SVR in the pooled Phase 3 studies.

You can see there's different resistant pathways for telaprevir failures with subtypes 1A and 1B. And in the light blue are the subtype 1A failures and the most frequent emergent substitutions, and this group were the V36M, R155K, or the double of these two.

In dark blue are the subtype 1 failures, where the most frequent substitutions were the T54A, S, V36A, A156T, S, or V. On the far right,

we also found that about 1 percent of 1A failures had the D168N substitution, which conveys cross-resistance to other macrocyclic protease inhibitors.

We looked at the persistence of telaprevir substitutions at the end of the Phase 3 study. So these were subjects who have failed the telaprevir-containing regimen in the Phase 3 trials. They were followed at multiple time points after telaprevir failure off-treatment to assess the persistence of the substitutions at the end of the study. After median follow-up of 45 weeks, 40 percent of the subjects had detectable resistant variants by population sequencing by the end of the study.

On the right side of the graph, you can see that 50 percent of subjects with subtype 1A in light blue had detectable substitutions at end of study, and these were the V36M or A and the 155K. About 20 percent of subjects with subtype 1B -- I guess it's sort of more in purple; on my screen it's dark blue -- were still detected by the end of

study, and these were the V36A, T54, but the A156T had gone away.

Vertex has already described study 112. And in this trial or in this study, 56 subjects were followed off-treatment for persistence of resistant variants after failure on telaprevir in the Phase 2 trials. Follow-up periods ranged from 5 to 40 months, with a median of about 25 months.

The denominators reflect the numbers of subjects with an available sample. And you can see that at six months, which is I guess the far left, grayish-looking bar, a high proportion of V36, T54, R155, and A156 substitutions persisted.

All variants were still detectable in some subjects at 24 months, which is sort of the bluish-green. And by 36 months, shown in light green, most variants had fallen below the level of detection by population sequencing. However, the R155K variant was still detectable by population sequencing at 36 months in 3 percent of subject isolates.

Prior null responders in study C216:

70 percent of the subjects who did not achieve an SVR in that study were prior null responders. Here are the rates by the treatment arms, and you can see they're fairly similar. And of these prior null responders who did not achieve an SVR, 80 percent of them had treatment-emergent telaprevir substitutions.

So the virology summary: Treatment-emergent substitutions emerged in the majority of isolates from subjects who did not achieve an SVR. There's divergent resistant pathways, depending on subtype. More failures were subtype 1A and null responders. Some substitutions can persist upwards of 2 to 3 years, especially the R155K. And we don't know yet if these substitutions will affect future treatment options.

Nobody's interested in IL28B, and people are pretty familiar with the 60 SNP, which strongly determines the outcome of HCV therapy and three genotypes of CC, CT, and TT.

The applicant obtained samples from about 1374 subjects from their Phase 2 and 3 trials, and

a retrospective sub-study on populations from about 975 samples from subjects in studies 108 and C216 was conducted. I'm going to show you the sub-study results, but just to let you know that the treatment effects in the sub-study were generally comparable to the overall population.

For naives, the addition of telaprevir increased the SVR rates across all three genotypes compared to peg and ribavirin alone. And you can see that there's a suggestion here that the T12 regimen may be better for CT and TT subjects compared to T8.

In treatment-experienced subjects, again, the addition of telaprevir substantially increased the SVR rates of all genotypes relative to retreatment with peg and ribavirin alone. And here we didn't really see any major differences between the immediate and delayed start of telaprevir.

So, in general, the results are consistent with previous reports of IL28B genotype effects on peg and ribavirin responses, and that CT and TT subjects had lower SVR rates in the peg/ribavirin

arms, and telaprevir increased the SVR rates in both treatment-naive and treatment-experienced subjects across all three genotypes compared to peg and ribavirin.

It's important to point out that this was a retrospective subgroup analysis. Subjects were not stratified at the beginning of their studies by genotype, and in some groups the sample size was rather small. Further, this cohort may not be fully representative of the overall population of chronic hepatitis C patients as there is a minimal contribution of samples from black subjects.

Overall, telaprevir increased the SVR rates by anywhere from 28 to 40-plus percent compared to peg and ribavirin across a broad range of disease and demographic covariates, including age, sex, body weight, race and ethnicity, geographic location, genotype subtype, high versus low baseline RNA, and cirrhosis. But we wanted to review the results of some important subgroups of interest, including blacks, Latinos, and subjects with cirrhosis.

So overall, about 9 percent of subjects in the telaprevir arms of the Phase 3 trials were black, compared to about 8 percent in the peg and ribavirin groups. In general, the SVR rates for telaprevir-treated subjects was 30 percent higher than those treated with peg and ribavirin.

In the table, you can see the total -- you can see the distribution in the top half of the table by naive versus experienced, so about 11 percent of naive subjects and 4 percent of experienced subjects in the telaprevir arms were black. The overall SVR rates were, for naives, about 10 percent lower than Caucasians, and for experienced, they were very close, at 63 and 65 percent.

This table shows the proportion of naive blacks who achieved an eRVR and their SVR compared to Caucasians. So in the top box, about 45 percent of blacks compared to 63 percent of Caucasians in the two naive trials achieved an eRVR. And of those, you can see the SVR rates were 76 percent for blacks compared to 87 percent for Caucasians.

So overall, in experienced subjects, the SVR rates were similar to Caucasians. In naives, the eRVR and SVR rates were lower than Caucasians, which is fairly consistent with previous peg and ribavirin trials, but still looks pretty encouraging. However, for some of these groups, the numbers of subjects was again kind of small.

For Latinos, 10 percent of telaprevir and 12 percent of peg/ribavirin subjects were Latino. In naive trials, it was 10 versus 11 percent, and in experienced trials, it was 10 versus 15. The overall SVR rate was 40 percent higher for telaprevir compared to peg and ribavirin. In treatment-naive subjects, the SVR rate was just a little bit lower in treatment-naives for Latinos, and in treatment-experienced, it actually was just a little bit higher. So it was pretty much comparable.

Treatment-naive subjects with cirrhosis, overall, about 9 percent of the telaprevir subjects and 6 percent of peg/ribavirin subjects were cirrhotic at baseline. For the naive trials, the

top part of this table shows study 108. There were 47 subjects enrolled, 26 to the T8 group and 21 to the T12 group. You can see the eRVR rate for the T8 and T12 were 42 and 43 percent, which is pretty comparable, and the eRVR to SVR rate was 64 percent for T8 compared to 78 percent for T12.

In study 111, 61 out of 530 subjects, or 11 percent, were cirrhotic at baseline. A total of 30 of them, or 49 percent, achieved an eRVR, which was fairly consistent with what was seen in study 108. And then these subjects were randomized, 18 to 24 weeks of peg and ribavirin and 12 to 48 weeks, and you can see the SVR rates on the right, 67 percent for the 24-week group, which is sort of consistent with what we saw in study 108. But for the T12 PR48 group, the SVR rate was much higher, 92 percent. So there's a suggestion for an improved SVR with 48 weeks of peg and ribavirin. And again here, the numbers of cirrhotic subjects in some of these groups is very small.

This is treatment-experienced subjects with

cirrhosis. As the applicant pointed out, about a quarter of the subjects in this trial -- this was C216 -- were cirrhotic at baseline. The numbers suggest a substantial benefit for prior relapsers, 87 versus 13 percent. For prior partial responders, it's a moderate benefit of about 14 percent improvement. But for prior nulls, it's only about a 4 percent improvement. So it's a fairly minimal benefit. But again, in some of these groups, the numbers were rather small.

I'll switch over to the safety review. As you heard, 3800 healthy and infected subjects have been exposed to at least one dose of telaprevir. In the Phase 3 trials, about 1800 were treated with telaprevir, a little over 1400 with the T12 regimen with peg and ribavirin for either 24 or 48 weeks, and about 364 subjects were in the T8 plus peg for 24- or 48-week group, and 493 subjects were randomized to peg and ribavirin. Because telaprevir is given for a fixed period, we primarily focused our review also on the telaprevir placebo dosing period.

Rash and pruritus you've heard a lot about. It was identified in the Phase 2 trials. A detailed monitoring and management plan was put into place for Phase 3. You've heard about the rash special search criteria. Severe rashes and rashes that led to discontinuation were considered events of special interest. And there was a dermatology expert panel convened to retrospectively adjudicate cases.

Rash events: 56 percent for telaprevir subjects versus 34 percent for peg/ribavirin. There were more grade 3 severe rash at 4 percent versus less than 1 percent. About 1 percent of telaprevir subjects had a serious adverse event of rash compared to no subjects treated with peg and ribavirin. The rash event of special interest was 7 percent compared to less than 1 percent.

Pruritus by itself was reported in about 47 percent of subjects compared to 28 treated with peg and ribavirin. And when you looked at rash and/or pruritus, it was 73 percent for telaprevir versus 48 percent for peg and ribavirin.

Rash was managed a number of ways, as you've already heard. About 7 percent of subjects actually discontinued telaprevir due to rash compared to less than 1 percent who discontinued placebo. Just under 1 percent discontinued the entire regimen compared to no subjects in peg and ribavirin.

Use of oral antihistamines, topical steroids, and systemic steroids were higher for treatment of severe rash among subjects who were treated with telaprevir. And in this group, there were a number of subjects who received more than one intervention.

You heard about the dermatology expert panel. And their conclusions were that this rash was clinically and histologically similar to peg and ribavirin. It was a pruritic, eczematous, spongiform dermatitis with lymphocytic perivascular infiltration. However, it was more severe and more extensive, and did occur at a higher incidence.

The majority of evaluable rashes by the expert panel involved less than or equal to

30 percent of the body surface area, but investigators frequently estimated the extent of body surface area to be greater.

In general, the rash improved after discontinuation of telaprevir, but it could take up to weeks to resolve. And less than 1 percent of subjects experienced suspected -- I'm going to induce another new term -- SCAR, which is severe cutaneous adverse reactions. And those are things like SJS, TEN, and DRESS. And as you heard, there were no cases of TEN. And among the cases of SJS or DRESS, there were no fatal outcomes. All subjects recovered.

We obtained a consult from our colleagues in the dermatology division, and some of the issues that were identified include that there needs to be a distinction between severe rash and SCAR, and that distinction is important because SCAR has implications for morbidity and mortality that may not attach to severe. So, for example, someone could have severe acne, but it's not necessarily a SCAR event.

Most SCAR events, particularly as they relate to DRESS, were suspected on case review, retrospective case review by the expert panel and not by investigators, which may actually suggest under-reporting and under-diagnosis of these events in the field. And the detection of suspected SCAR cases may be noteworthy given that SCAR are generally considered to be rare, and the sample size of clinical trials intended to support marked improvement are generally not powered to detect such rare events.

We also feel that the expert panel review may have been biased towards characterizing only the more severe events, given the definition of "event of special interest." So the extent to which the conclusions about eruptions from the expert panel review might apply to the broader population of telaprevir-treated subjects who experienced cutaneous eruptions is unclear. And most of the ESI events had what we considered an eczematous component, so it's not clear that this translates to a general characterization of the

rash as being primarily eczematous.

So in summary, telaprevir-related rash and pruritus occur frequently. They can be severe and treatment-limiting. SCAR events occur infrequently but may be significant. They may have been under-diagnosed by investigators. It's important to recall that not all severe rash were SCAR events. And in the subjects who had SCAR events, there were no deaths. Rash may take weeks to resolve. The effect of antihistamines and steroids remain unclear. And as you also heard, the etiology of this rash remains undetermined.

Anemia. Again, we've heard a lot about anemia. It's the most problematic side effect of ribavirin. We know the onset of rash in subjects treated with telaprevir is faster and that telaprevir increases the decline in hemoglobin levels by a gram to gram and a half above what's observed with peg and ribavirin.

Management. Prospective management was ribavirin modifications and/or telaprevir discontinuation. Again, no dose adjustments of

telaprevir for anemia were allowed, and as you've heard, use of erythropoietin-stimulating agents was generally prohibited. And the applicant also put together another one of these special search criteria to capture the various descriptive terms and events used by investigators to characterize anemia.

Again, we had some challenges such as looking at differences in sex and baseline hemoglobin levels. But what we did find is that for any anemia special search criteria event, it was 36 percent of subjects treated with telaprevir compared to 17 percent treated with peg and ribavirin. There were more grade 3 events, more SAEs.

More subjects had a shift to greater than or equal to grade 3 reductions in hemoglobin using the DAIDS grading scale. Absolute reductions to below 10 was about 37 versus 15 percent, and hemoglobin reductions to below or equal to 8.5 grams per deciliter were higher in telaprevir at 10 compared to 3 percent in the peg and ribavirin group.

We looked for clinical events possibly associated with anemia. There were 3 events of myocardial infarction in telaprevir subjects. None of these subjects had anemia. Two had significant coronary artery disease at the time of their MI. One unfortunately died. One discontinued his study medications, recovered, and resolved. And one, who had an anterior MI, continued dosing and completed the study.

Things like angina, dizziness, dyspnea, syncope, we didn't find any important differences between treatment groups based on the presence of anemia. There was more fatigue in subjects who received telaprevir, but it didn't appear that every one of those was associated with anemia.

Management of anemia. Again, 4 percent of subjects discontinued telaprevir. Ribavirin dose reductions were more frequent in the telaprevir group, as were ribavirin dose interruptions. About 2 percent of subjects in the telaprevir group had to discontinue ribavirin; 1 percent discontinued all medications in the regimen. You've heard about

the 6 percent who received the blood transfusion. And the ESA use was right about 1 percent per treatment group.

Ribavirin modifications/interruptions really had little effect on the SVR rates. But if you had to stop ribavirin and telaprevir, there was a much greater negative effect on SVR rates.

We looked at the outcomes of subjects who received blood transfusions, and actually 59 percent of the subjects who received a blood transfusion were able to go on and achieve an SVR. And of the 24 subjects who received an ESA in the telaprevir group, 14, or 58 percent, achieved an SVR.

So in summary, telaprevir anemia occurs frequently. It can be severe and treatment-limiting. It's manageable through discontinuation of telaprevir and ribavirin dose reductions, interruptions, or discontinuations. I didn't show you this, but it was more frequent in females, a little bit older age people, people with lower BMI and cirrhosis, and that's basically consistent with

what's been seen in prior peg/ribavirin studies. And anemia-associated clinical events were generally comparable between the treatment groups.

Anorectal disorders you heard a little bit about, 29 versus 7 percent. The most commonly reported were hemorrhoids, anorectal discomfort, and anal pruritus. Less than 1 percent were serious, less than 1 percent were severe, and there were 7 events that led to discontinuation of telaprevir. They seem to be fairly well managed with local and topical agents, and we still don't have a mechanism for this toxicity.

All the adverse drug reactions in the database were essentially consistent with the profile in peg and ribavirin. Events that occurred in at least 20 percent of subjects in all treatment groups included rash, fatigue, pruritus, nausea, headache, anemia, diarrhea, flu-like symptoms, insomnia, and pyrexia.

This table shows the frequency of events that -- or the events that occurred at a frequency of at least 5 percent more amongst subjects treated

with telaprevir. We've already talked about rash and fatigue and pruritus and anemia and the anorectal stuff. There was more GI events, such as nausea, diarrhea, and vomiting, and again, subjects didn't seem to like the taste of telaprevir, so there was more dysgeusia.

We looked at the hematologic abnormalities, primarily grade 3 or greater, to see if there was any differences, and we found that total white count reductions were a little bit more in telaprevir. But when you look at the absolute neutrophil count reductions to grade 3 levels, it was more often in the peg and ribavirin group. Absolute lymphocyte reductions to grade 3 levels was much higher in telaprevir, at 18 versus 6 percent, and reductions in platelet count to above grade 3 levels was 3 percent versus 2 percent.

We again looked for clinical events that might be associated with these abnormalities. And it is difficult to count clinical events based on lab values, as investigators report things

differently and may have reported isolated asymptomatic lab abnormalities as a clinical event.

We looked for neutropenia as a clinical event, and it was actually reported more often in peg and ribavirin subjects than in those who received telaprevir. There were two telaprevir subjects who had events of febrile neutropenia, but neither one had an infection. And there were no other cases of serious infections related to low white cell count. Colony-stimulating factor use was about 1 percent in both treatment groups.

With regard to lymphopenia, we looked for serious opportunistic infections that might have been associated with low lymphocyte counts. There were none. Thrombocytopenia, the frequency was generally comparable.

There was one life-threatening event in a telaprevir subject who presented with epistaxis and purpura and a platelet count of 10,000. The subject was treated with ethamsylate and prednisone, and then asked to be discharged from the hospital and was lost to follow-up. So we

don't have any follow-up on that patient. But no subjects in any of the treatment groups received a platelet transfusion.

Another lab abnormality we noted was uric acid elevations. They were noted in Phase 2, and in the Phase 3 trials they were substantially higher in telaprevir compared to peg/ribavirin subjects at 73 versus 29 percent. They seemed to follow a similar pattern as other labs associated with telaprevir. There was a steep increase during the first couple of weeks, levels peaked and then stabilized, and then within about 8 weeks after cessation of dosing with telaprevir, were back to levels comparable with peg and ribavirin.

Thirteen subjects experienced clinical gout or gouty arthritis, 11 in the telaprevir group versus 2 in the peg/ribavirin group; 7 of the 11 events in telaprevir occurred during telaprevir dosing period. Only one of those subjects had a previous history of gout. Subjects generally were treated with colchicine, indomethacin, hydration, ibuprofen, and all subjects recovered. There were

no SAEs and no discontinuations.

Bilirubin elevations were much higher in telaprevir versus peg/ribavirin at 41 versus 30 percent. Elevations to above grade 3 levels, which was greater than about 2.6 times the upper limit of normal using the date scale, were 4 percent for telaprevir, 2 percent for peg and ribavirin. Again, the steepest increase very early, then there was stabilization, and by weeks 12 to 16, they were back to baseline levels.

About 1 percent of subjects in both treatment groups had a "clinical event." Again, this could have been an isolated lab abnormality. And 14 of these telaprevir subjects only listed -- the only thing that was listed was either elevated bilirubin or hyperbilirubinemia. Thirteen of the 14 actually occurred after the telaprevir dosing period was completed.

There were two subjects that had ocular icterus, and one of those subjects discontinued. And one of the 14 subjects had a history of Gilbert's disease and had jaundice.

In the peg and ribavirin group, the three subjects, there were 2 with just increased bilirubin and one that had increased bilirubin with jaundice.

So, to conclude, with efficacy, telaprevir and peg and ribavirin significantly increased the SVR rates compared to peg/ribavirin alone across a broad range of populations and demographic subgroups. In treatment-naive subjects, there was significantly increased eRVR and resultant SVR rates, which demonstrate that the duration of therapy can be truncated in early responders without jeopardizing efficacy.

The T12 regimen was more efficacious than T8, but may be associated with an increased risk of anemia and rash. There was no apparent increase in efficacy for 48 weeks of peg and ribavirin in early responders. And peg/ribavirin for 48 weeks did appear to provide an additional benefit in subjects who had not achieved an eRVR.

In treatment-experienced subjects, the T12 PR48 regimen was superior compared to retreatment

with peg and ribavirin for all treatment groups. We found no important differences between the delayed or immediate start of telaprevir. And the T12 PR24 regimen may be acceptable for prior relapsers who achieve eRVR, as you heard Dr. Jadhav tell you.

For the subgroups of blacks, Latinos, and cirrhosis, across all of them there were increased responses compared to peg and ribavirin. For blacks, there were lower SVR rates in naives compared to Caucasians, consistent with prior PR studies. Latinos had pretty much similar responses to Caucasians. And in cirrhotics, there was a suggestion of an added benefit for longer duration of peg and ribavirin in naives and a suggestion of minimal added benefit for null responders. Many of these results are encouraging, but, again, there were small numbers of subjects in some of these subgroups.

Virology. On-treatment virologic failure is associated with the presence of resistant substitutions, more subtype 1A and prior nulls

failed treatment. There was divergent resistant pathways, depending on the subtype. Some mutations, such as the R155K, may persist for upwards of 3 years, and so the impact on retreatment is currently unknown.

The pharmacogenomic post hoc analysis of IL28B data suggests improved SVR rates for all genotypes treated with telaprevir, but may need prospective confirmation with a more representative population.

Safety. Rash and pruritus can be severe, treatment-limiting, but manageable. Not all severe rash were SCAR events, and SCAR events did occur but there were no deaths.

Anemia can also be severe, treatment-limiting, but also manageable with telaprevir discontinuation and/or ribavirin modifications. We didn't really see a signal for increases in clinical events related to anemia. Anorectal disorders occur frequently, primarily are bothersome and appear manageable.

We saw a few more GI events of nausea,

vomiting, diarrhea, and dysgeusia with telaprevir. There was a low frequency of other hematologic abnormalities. Elevated uric acid levels, possibly related to anemia-related red cell breakdown. And the elevated bilirubin levels may be partially explained by a similar mechanism, but we're still looking at them to make sure we don't miss something else. And that is it.

Thank you.

Clarifying Questions from Committee to FDA

DR. CARGILL: Thank you.

Clarifying questions from the committee for the FDA? We'll start with Dr. Clay.

DR. CLAY: I guess the first is just a comment. I have a hard time hearing presentations about dermatology, and your making an abbreviation of a multitude of symptoms and calling it SCAR, because in my mind, a scar is a certain dermatological condition. So that's neither here nor there.

I have a question that relates to how well the study was blinded. These were blinded studies

done?

MR. FLEISCHER: 108 and C216 were blinded; 111 was open label.

DR. CLAY: Okay. So my question to that is, you're conducting a blinded study in which you had a significant difference in rash from one group to the next. So I guess that's okay if nobody knew that there was the likelihood of a rash occurring.

I was just curious, when the sponsor submitted their material, did they discuss in there how it was managed at the investigator level?

MR. FLEISCHER: The rash?

DR. CLAY: No. The determination as to whether the rash was possibly or probably related to study medication.

MR. FLEISCHER: I think that was in the rash management program.

DR. CLAY: Okay. And that was --

MR. FLEISCHER: It was in the protocol describing how rash should be assessed and managed, that was given to every site, yes. But Bob can --

DR. CLAY: No, no. I'm not asking about

management. I'm asking about the determination in the reporting to the sponsor as to whether or not the investigator felt the rash in and of itself was related to study drug.

DR. KAUFFMAN: Yes. During the blinded phase, of course, no one knew what the treatment assignments were. The investigators used their judgment to decide whether it was related or not to the treatment that was occurring.

DR. CLAY: But rash was included in the investigational drug brochure provided to the investigators when they were considering taking on this study?

DR. KAUFFMAN: Yes. And by Phase 3, there was general acknowledgment that rash was associated with telaprevir, and it was certainly in the investigators brochure.

DR. CLAY: Okay. That's fine. We've been through efavirenz. We understand how to deal with that, and nevirapine and the others.

My next question actually relates to a different way -- maybe it also relates to blinding

as well. We talked about an increase in bilirubin within the first two weeks in a fair number of patients. When that sample is drawn and separated, as you need to separate out your samples in order to do viral loads, you're going to see a nice, pretty, yellow color.

I'm wondering, did your placebo color your plasma yellow?

DR. KAUFFMAN: I'm not aware whether it did or not.

DR. CLAY: Because you're going to spin it down in a serum separator tube to send it off, and you're either going to have a yellow tube or not. If you did not blind -- or unblind and mandate unblinding at the site level for your lab processing personnel, I'm questioning the validity of your blindness.

DR. KAUFFMAN: I mean, I think in most cases the bilirubin levels were not markedly elevated. Therefore, it's highly unlikely the plasma would actually be icteric.

MR. FLEISCHER: Yes. Only about 4 percent

were above grade 3, so the majority of those were grade 1 and grade 2. And so --

DR. CLAY: Yes. Icteric is a clinical presentation, as I understand it. Now, my disclaimer, I'm just a pharmacist. But I have processed atazanavir drug before, or atazanavir-containing plasma before, and the patient didn't have to be clinically icteric in order for me to see the yellowing of the serum.

MR. FLEISCHER: The other thing is, like I said, some of these were individual spikes. Not everybody fit this pattern. Some were asymptomatic. They presented. They got a lab. It was a grade 2 level, and it was called hyperbilirubinemia. And then it went down at the next lab. So we can't say that everybody went up, persisted and then went down. They were all over the place.

DR. KAUFFMAN: Also, bilirubin levels were also elevated in the placebo subjects, as you saw. It's not very likely that someone, without knowing what the treatment assignment was, would really be

able to assign a treatment assignment based on the color of the plasma because elevations occurred in the placebo subjects as well as in the telaprevir subjects.

DR. CLAY: Fair enough, 40 percent versus 20 percent.

DR. KAUFFMAN: Yes. But those are both high, so in any individual case, it would be hard I think for someone to ascertain that. And I think, also, just to go back to your question about rash, as you saw, the rates of rash were quite high in the control arm as well as in the telaprevir arm. True, they were higher. But overall across the study, rash was occurring quite frequently.

Therefore, again, because of that, we think it's less likely that a patient could be unblinded as to their treatment assignment just by the occurrence of a mild or moderate rash because 30 percent of the control patients had mild or moderate rash. So we felt that, as best we could, that the blind would be maintained.

DR. CLAY: Thank you.

DR. CARGILL: Dr. Lewis, you wanted to join in?

DR. LEWIS: I was just going to point out that same fact, that we really did not think the blinding was affected because the rates were high in both arms. In an individual patient, you wouldn't be able to predict which event was related to which drug.

DR. CLAY: And my final question relates to the statistical presentation that was up there. I'm not a statistician, but statistically, everyone who eats pickles dies. So I'm always questioning statistics.

You made a comment in your presentation, and it was that you assumed that the response for triple would be identical to the response for double. Does that take into account -- and I apologize if you said it and I missed it -- that you may have a change in dropout rate due to that third drug administration in a triple versus a double?

DR. JADHAV: I mean, it completely doesn't

take that into account. But the point is --

DR. CLAY: So no?

DR. JADHAV: Yes. No.

DR. CLAY: Okay. Does that invalidate your model?

DR. JADHAV: No. It's not a model, actually. It's not even any statistics. It's actually --

DR. CLAY: You had to calculate it for about 15 minutes, so I'm really hoping it was important.

DR. JADHAV: Yes.

[Laughter.]

DR. JADHAV: So while it does not per se fully account for everybody in that group, even if, say -- in fact it validates more than even the 44 percent of those responders that I talked about, even if 100 percent of them don't respond, that 44 percent goes down. So actually, that difference you see increases.

So 100 percent is actually -- if you think very carefully, it's a simple multiplication is the worst case. If patients drop out and don't

complete, the difference you see in the telaprevir arm of going from 54 to 44, which was 10 percent here, assuming 100 percent, that difference will increase.

So while it does not account to me, it's actually a worst-case estimate of who are those additional 10 percent patients. This makes sense because we have the SVR data from both arms. So even if I stake out, I don't have in front of me what's the percentage of dropouts due to, say, adverse event in telaprevir, the argument becomes even more convincing because the difference will become more than 10 percent. So those additional patients are the future relapsers that we are treating.

Does it make sense? There's no statistics here. Let me be very clear. It's a simple -- there are three steps: multiplication, addition, and division, and that's it.

[Laughter.]

DR. CLAY: And in the right combination, sir, that is statistics.

DR. CARGILL: I think we got this. We'll move on.

Ms. Dee?

MS. DEE: Okay. I'm not sure if this is for the sponsor or for the agency. I know I heard somebody mention prior rash in patients before, but I didn't really hear an answer about whether people who had had a rash situation in the past might be more susceptible to getting a rash with this drug.

DR. CARGILL: I think the sponsor can answer that.

DR. KAUFFMAN: I'll ask Dr. Singhal to come up and talk about that.

DR. SINGHAL: We did not collect information on baseline experience with rash. For example, in the treatment failure trial, C216, we did not exclude any subjects who had previously had rash.

However, when we collected the data on the rash events that patients experienced during the study, we did collect information as to whether they had had an event previously. And the rates that we observed in C216 were really no different

from rates in the 108 study. So we don't believe that there's an impact on prior rash. But to be really sure, we are collecting prospective information in ongoing studies, so we are looking at that in further depth.

I also just wanted to address a comment that was made earlier with regards to blinding. And I just wanted to say two things. One is that in our Phase 3 program, we collected rash data as events of special interest, as Dr. Fleischer pointed out, and these were collected in a blinded manner.

So if a physician felt that he needed to discontinue telaprevir because he had assessed it at greater than 50 percent body surface area, we simply collected that data and accepted it for what it was. We did not unblind any patients. And the DEP's review was a complete blinded review of 221 cases. There was no unblinding. The unblinding was done only at the end of the study.

MS. DEE: And I have a quick EPO question.

DR. CARGILL: I need to give a clarification instruction to the committee. This is the FDA

question period, so please make sure that your questions are directed to the FDA. We will have a chance to go back to the sponsor.

MS. DEE: All right. This is for the FDA.

On the anemia stuff, the sponsor provides -- I don't want to drill down too far -- data that talks about days to onset and the weeks it was stable, became stable, the weeks that it started to reverse back to baseline. Were you able to confirm that?

MR. FLEISCHER: Yes.

MS. DEE: Good. And this is for the agency as well, I guess more of a statement rather than a question. But all of these questions that we've been having about the number of blacks in trials, it's giving me deja vu. And I'm just hoping that we're not going to go through this again with these new drugs.

We need black people in these studies. There are plenty of black people with HCV, and unlike HIV, there's an absolute difference in what happens in people of color, Latinos as well. I

just really think that it's time for the agency to consider, like we saw yesterday, a cohort 1 and a cohort 2.

It's like the dentist. It's painful at first, but it's always worse if you wait. I mean, half of the questions that we have are like what do we do about these situations for black people that we don't have enough numbers to give us direction? So just hopefully it'll be different this time.

DR. BIRNKRANT: We agree with your comments. We, too, have discussed the situation with sponsors at very early phases of drug development, and then we're presented with a marketing application.

So on one hand, we could hold up a marketing application while we wait for more data in certain subgroups; or we can act on the marketing application and perhaps ask for additional data postmarketing, given that these are serious and life-threatening diseases.

But maybe if we say it publicly more and more, that the message will get across because we too share your frustration. And we also want to do

what's best for the public as well. So we hope all of the companies who are here and are listening to the webinar, pay attention to this situation.

DR. CARGILL: Thank you. And with that, we will turn to clarifying questions for the FDA.

Dr. Roland?

DR. ROLAND: Yes. I have a question about the creative approach to the prior relapse patients and response-guided therapy. I just wanted to clarify because it gets very confusing following these discussions, and my best understanding is that the data that you presented on actual subjects is the Phase 2 data.

It makes me really wonder why the Phase 3 studies, if there were compelling Phase 2 data – granted about 50 people -- why the Phase 3 studies didn't address that question specifically.

So I just want to confirm that my understanding is clear. And if you have any insight about why the Phase 3 study didn't address it specifically, I'd appreciate that as well.

MR. FLEISCHER: The data was from Phase 2.

But I think, as the sponsor said, they didn't have it all by the time they initiated their Phase 3 trials. So there wasn't sort of this expectation that it would work, and they didn't propose to study it. So this is sort of a -- yes. That's it.

DR. CARGILL: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: Yes. Dr. Fleischer, you confirmed what the sponsor said about the lack of impact of the dose reductions of ribavirin on the sustained response. You did also comment that the people who had to have it stopped did have a somewhat lower response rate.

I'm interested in whether you looked at this for the people who stopped treatment for the rash. There was a substantial proportion who had to terminate telaprevir treatment because of rash. I could not -- there was a plot that showed the onset, but that was for all rashes. I don't know whether the more serious ones occurred somewhat later. I don't know how many weeks of therapy they didn't get.

So that's my first question, is can you comment on the impact on response rate of the termination of therapy for rash?

MR. FLEISCHER: I can't. I don't know if the sponsor can.

DR. KAUFFMAN: One part of the question is, yes, it's true. Patients with severe rash generally tended to occur later during the 12-week period of telaprevir, so the impact on potential efficacy would have been less.

For example, when you look at the 8-week telaprevir arm, you can see that although there is a decrement in SVR compared to the 12-week arm; still they have a 72 percent SVR rate. So even if patients receive 8 weeks of telaprevir, they still gain substantial benefit from it.

DR. ELLENBERG: Okay. Of course, I don't know whether there's something special about the patients who had this severe rash. Maybe after lunch we can get that information about what actually happened to the ones who terminated in terms of their final outcome.

DR. KAUFFMAN: Their outcome?

DR. ELLENBERG: Yes.

DR. KAUFFMAN: We can try to get that.

DR. ELLENBERG: The other thing that I wanted to -- I'm not sure whether it's a question or a comment. But it has to do with this attempt to understand about what an RGT would be in the relapsed patients. And I'm just concerned that the presentation that we got seemed to make a very strong assumption that numbers like 54 percent and 44 percent were in fact truth.

I haven't seen very many confidence intervals in these presentations. But I don't -- you know, 54 percent here could be 49 percent at another time, and the 44 percent could be 48 percent another time. And I can't say I really totally followed this presentation, but at this point I don't really find it very convincing.

I would think that some good use of statistics might be helpful in terms of seeing what the effect of the variability on these estimates would do to the conclusions. You've lots of good

statisticians over there. I know that.

DR. CARGILL: Dr. Ghany?

DR. GHANY: Yes, thanks.

I have two questions. The first relates to anemia, and it's for the agency.

Did the agency look at classifying the severity of rash using the investigators' adjudication of severity? And how does that change the percentage of people who had grade 3 severe rash, instead of using the DEP's adjudication?

MR. FLEISCHER: We were using the investigators' assessment for our assessment of -- in the table, for events, those were investigator assessments.

DR. GHANY: So it wasn't the DEPs, then?

MR. FLEISCHER: No. No.

DR. GHANY: Okay. And the second question, I don't know whether this is more for the agency than the sponsor. So we were told that despite ribavirin dose reduction in almost a quarter of patients, it had little effect on SVR. So was any analysis done or consideration taken to starting

the ribavirin dose at a lower dose during the triple therapy period?

MR. FLEISCHER: Prior to the study initiating, about starting with a lower dose?

DR. GHANY: Starting with a lower dose.

MR. FLEISCHER: No. I don't recall having any of those discussions.

DR. CARGILL: If the sponsor could address that?

DR. KAUFFMAN: Just make a quick comment that, obviously, ribavirin is an approved drug for hepatitis C. In general, the advice we gave for physicians was to follow the label instructions for both peginterferon and ribavirin. Therefore, it was started at the usual dose based on weight and was adjusted according to the ribavirin package insert. So that's all we can say.

DR. CARGILL: All right. Thank you.

Dr. McGovern?

DR. MCGOVERN: I'm going to hold my question for the sponsor.

DR. CARGILL: Thank you.

Dr. Van Dyke?

DR. VAN DYKE: Yes. Regarding the differential response by race and gender, I wonder how much of that can be accounted for by the IL28 genotype. And I also wondered, is there a relationship between the IL28 genotype and cirrhosis? Could that be a confounding variable there as well?

DR. PACANOWSKI: Mike Pacanowski, genomics group.

Concerning the IL28B relationship with race, yes, it is. The T allele is more common in black subjects. In these trials, there were very few black subjects enrolled overall, let alone included in the generic sub-studies. So it's close to impossible to make any assessment concerning that.

We expect the IL28B genotype to be independent of sex or gender. So, again, there wouldn't be any explanation of the response there, either.

DR. VAN DYKE: Cirrhosis?

DR. PACANOWSKI: Cirrhosis? So for the

treatment-naive trial, we did not have complete clinical data because it was a de-identified data set because it was voluntarily collected generic information. So we were not able to compare things like cirrhosis across the different genotype groups.

I do believe in the treatment-experienced trial, C216, that cirrhosis rates were similar across the genotype groups, but I'd like to check that, or perhaps the sponsor can clarify.

DR. CARGILL: Thank you.

Dr. Knodell?

DR. KNODELL: I have two questions. The first one relates to this ribavirin. I think this is really an important clinical point.

When we make dose reductions with ribavirin, we try and do it later in the treatment. If you can carry these people out 16 or 17 weeks and then cut your dose, they seem to do better. There's no question that ribavirin reductions decrease SVR.

Now, you made a statement, Dr. Fleischer, that there was no decrease in SVR with ribavirin

decreases or reductions, but we didn't see any data to support that. And when I look at their anemia timeline, the timeline of anemia is fairly quick. It's during the first 4 to 12 weeks of treatment than both groups. And the majority of the anemia is due to ribavirin. There is an incremental increase with the telaprevir, but certainly ribavirin would probably be the drug that we'd want to start reducing rather than stopping the telaprevir, if I'm a clinician out in the real world taking care of these patients.

So I wondered if you could expand, what is your basis for saying that ribavirin reductions did not decrease SVRs? And what was the timing of those ribavirin reductions when they were made?

MR. FLEISCHER: I'd have to go back and look at the timing. But we found -- let's see. It says, "Among subjects who underwent a dose modification or interruption of ribavirin, a temporary interruption, the SVR rate went down to about 73 percent in naives and about 77 percent in experienced subjects overall."

So there was a little bit of a -- I forget what the --

DR. KNODELL: We didn't see that data.

MR. FLEISCHER: I know. I have it in case you want it.

DR. KNODELL: All right.

MR. FLEISCHER: But just doing things like reducing the dose of ribavirin, interrupting it or discontinuing, can decrease the SVR rate from about 75 percent to about 40 percent in naives, and from about 65 percent to about 20 percent in treatment-experienced subjects.

So taking the ribavirin away had a much bigger impact than trying to keep some ribavirin on board. And we saw from the Phase 2 trials, where there were ribavirin-sparing arms, that they didn't really actually respond better than control, peg/ribavirin arms. So I think there was an attempt to try to keep patients on ribavirin as best as possible. But it is what it is.

DR. KNODELL: My second question relates to cirrhosis. The sponsor, in data that they

provided, said that they only -- the accession was for cirrhotics A and B because there was decreased telaprevir exposure, 15 percent in cirrhotic A, class A, Child-Pugh class A, and 53 percent in Child-Pugh class B, and not to use this drug in Child-Pugh class C.

Now, we've not had any breakdown in your data on cirrhosis, which class these were. So my question is, generally, if you've got a drug that's metabolized by the liver, when you've got liver disease, you have increased exposure. Unless this is a pro drug, telaprevir, which I don't believe it is, I'm not quite sure why there should be decreased exposure in cirrhotics.

Then my question is, do any of your cirrhosis data that we have seen today break the cirrhotics down as to whether they're A, B, or C, or can we just assume that there weren't any class C cirrhotics in the trial?

MR. FLEISCHER: They were all supposed to be -- they were all compensated, and they all looked like they had normal synthetic function. So

we didn't parse them out by A, B, or C. They were all supposed to be pretty well compensated.

DR. ROBERTSON: Just to address the decrease in exposure, we have seen this with other hepatically metabolized drugs, but not typically. You're right. Some hypotheses might be related to protein binding, less protein binding in these more severely impaired patients, though in this study there was some problem with assessment of protein binding so we can't use that -- but that's a hypothesis -- as well as decreased absorption might be another contributor to the lower exposure.

DR. KNODELL: So that's just AUC? When you say "exposure," you're looking at AUC?

DR. ROBERTSON: AUC. Exactly, yes.

Oh, sorry. Sarah Robertson, FDA.

DR. CARGILL: Thank you.

Dr. Strader?

DR. STRADER: I want a clarification question answered on the rash. I keep hearing that there was a whole bunch of people who discontinued as a result of rash, but I see in your slide

number -- hang on -- 35, it says less than 1 percent of patients in the telaprevir PR group discontinued treatment because of rash. Is that correct?

MR. FLEISCHER: That was less than 1 percent who discontinued the entire regimen. But 7 percent stopped telaprevir and may have continued on peg and ribavirin.

DR. STRADER: And ribavirin. Okay.

My last question, you talked about dermatologic issues that needed to be identified, and you said distinction between severe rash and SCAR, but you don't tell us what that distinction should be, how do you define this SCAR. Because if you don't tell us, how are we going to know?

Have you decided yet, or it's something --

MR. FLEISCHER: Well, SCAR events, maybe Dr. Bigby can say something. But SCAR is sort of a specific definition that's associated with morbidity and mortality. Things like the DRESS is a SCAR. SJS is a SCAR. TEN is a SCAR.

DR. STRADER: But there have to be some

distinctions, something that you find, bullae, something that tells me this is SCAR as opposed to just a maculopapular rash.

DR. CARGILL: I think perhaps we can ask Dr. Bigby to clarify that for us.

DR. BIGBY: I think that the rashes that would be considered severe and sometimes life-threatening would be toxic epidermal necrolysis; Stevens-Johnson syndrome, which most people think those two are related and only depend on extent.

The big thing about those two are that they lead to epidermal detachment, so that if there's more than 30 percent epidermal detachment, you would call it TEN. If the epidermal detachment is less than 10 percent, it's SJS. And if it's somewhere in between, there's an overlap syndrome.

Then patients that have what's referred to here as DRESS have actually an exanthematous eruption that usually covers more than 50 percent of the body, associated with eosinophilia and systemic symptoms, the most common one being fever. And they can also have internal involvement of

other organs like liver and kidneys. It, too, has a mortality associated with it.

So those are the ones that I think he is referring to when he says SCAR.

DR. STRADER: So anything else is a severe rash. TEN, SJS, and DRESS, and the overlap thing would be considered SCAR, but everything else would be considered regular rash or severe rash?

DR. BIGBY: That's usually the case.

DR. STRADER: Okay. Thank you.

DR. CARGILL: Thank you, Dr. Bigby.

Dr. Korman?

DR. KORMAN: I have a question for the agency. In slide 54, you conclude that the rash is severe, treatment-limiting but manageable. And when I get to look at slide 39 -- and remember, a lot of us are gastroenterologists, hepatologists as well; we're good at recognizing polyps, but we may not be that good at recognizing rashes -- the rashes are severe and treatment-limiting. They're under-diagnosed by the investigators. They take weeks to resolve, which I assume produces some

morbidity. We don't know how to treat it; antihistamines and steroid therapy is unclear. And we have no idea what causes it.

So I don't know how that manageable fits in to that slide because we don't have MGH dermatologists available on-call when we confront these things. So I'd like to get some comment about that manageability issue.

MR. FLEISCHER: Well, we're working it out. But if nothing else, you can stop the telaprevir. So that's pretty manageable. If you can get them out to 8 to 12 weeks, you've got a pretty good chance of either completing therapy or still having a pretty good SVR rate. If it happens really early and you have to stop, it doesn't say you have to stop peg and ribavirin.

So from a very sort of simplistic approach, stop the telaprevir. For more convoluted approaches, we're trying to figure those out with our derm consultants, and how would we convey that kind of a message in a label for a clinician to say, okay, if this rash hits this much, these are

the options available to me to manage it. And we have some ideas.

DR. KORMAN: It's clear when the hemoglobin reaches a certain level or where the neutrophil count reaches a certain level; it's not clear about rashes. And "tough it out" isn't something that patients want to hear.

DR. CARGILL: Thank you.

Dr. Lewis?

DR. LEWIS: I would just point out that even though the dermatology expert panel thought that there may have been some under-diagnosis of these cases of DRESS or SJS, they were in relatively -- they were very rare. There were single digits out of a program of 3800.

While that's not insignificant, if it was under-diagnosed, the management plan that was provided in the Phase 3 protocols seemed to allow patients to recover without serious sequelae, and in many cases complete their treatment. So the management plan that was used in the Phase 3 program appeared to be effective.

DR. CARGILL: Thank you.

Dr. Bigby?

DR. BIGBY: My question for the agency is, were you given the details of the three suspected cases of SJS and the 11 suspected cases of DRESS, and did you come to any conclusion about whether those diagnoses were correct? And of the ones that were correct, were they drug-related?

DR. CARR: I'm Brenda Carr, dermatology. And we were in agreement with the dermatology expert panel in their assessment of the suspected cases of SCAR. The cases were generally considered treatment-related, is my recollection, except for one case of Stevens-Johnson syndrome, which occurred, I believe, 11 weeks after treatment was discontinued, so was therefore not thought to be telaprevir-related.

DR. BIGBY: So that means that -- so two of the suspected cases of SGS you concluded were cases of SGS, and that they were related to telaprevir?

DR. CARR: I believe one case was definitive. And again, that was the case that

occurred some weeks post-treatment. I don't recall whether the other two were possible or probable.

I'm sorry. Could you repeat the question again?

DR. BIGBY: So there are listed three suspected cases of SJS.

DR. CARR: Yes.

DR. BIGBY: So the first part of the question is, did those patients have SJS or not?

DR. CARR: Yes. They were suspected to. The adjudication was based on a review of photographs and not on actual assessment of the patients or subjects. So based on a review of their photographs, conclusions were reached that the subjects were suspected to have Stevens-Johnson syndrome.

DR. BIGBY: And how about for the 11 cases of DRESS? Your conclusion was that they actually did have DRESS?

DR. CARR: They were suspected to have had DRESS, not definitive. Not all of them were definitively determined to have DRESS. And I could

follow up with you on specifics of the breakdown.

DR. CARGILL: If you could do that, that would be appreciated.

We will now break for lunch. We'll reconvene again in this room in one hour from now, which is at 1:00 p.m. Please take any personal belongings you want with you at this time. The ballroom will be secured by the FDA staff during the lunch break.

Panel members, please remember that there should be no discussion of the meeting during lunch amongst yourselves or with any member of the audience. Thank you.

(Whereupon, at 12:03 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

[1:00 p.m.]

Open Public Hearing

DR. CARGILL: Good afternoon.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing of the advisory committee, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee

if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments that you provide can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

One other note, please. Because we have a number of speakers, your time will be 4 minutes. Your microphone will be cut if you exceed that time. Thank you.

Martha Saly?

MS. SALY: Good morning -- good afternoon, I guess. Thank you for inviting me to speak once again today. As you might remember, I spoke yesterday, and I'm the director of the National Viral Hepatitis Roundtable, which is a coalition of about 175 public and private organizations that are dedicated to the elimination of viral hepatitis in the United States. Vertex Pharmaceuticals is a member of NVHR, and they have been a funder of NVHR, but they did not pay me to attend these proceedings today.

Dr. Cargill, yesterday I was really touched by your statement about bringing new hope to your patients. And I really wanted to speak again today from the point of view of being a patient and talk about the many patients who have come to me looking for new hope in treatments because treatments have previously failed these patients.

So I wanted to just talk about how -- I understand that these treatments are still going to be difficult for patients. They are still going to

be based on interferon and ribavirin, and that is a concern to me. But I still think that the new treatments will create a real watershed event in this country, and it will be monumental what we can do with these treatments available to the patients who have been failed before by our efforts.

Dr. Friedman, you also noted yesterday that someone might need the wisdom of a Talmudic scholar to be able to prescribe these treatments, and I realize that that's also a concern of this committee. I would ask you if that might have also been the same in the past with HIV treatments, and yet many dedicated providers stepped up and started treating their patients with HIV. And in fact, many of those providers went on to be our champion providers for patients with hepatitis C.

I think that that is going to be quite possible for the many dedicated providers who want to do something for their patients who have been suffering with hepatitis C for far too long.

I think that if the influx of patients is anywhere near as great as we expect, that as the

community works to amplify awareness and screening efforts in conjunction with the new therapies, it will be very imperative for the labeling of these products and the medical provider education materials to be carefully constructed in order to make prescribing of these drugs an option for a wide group of providers and their patients, and not just a handful of specialists that we've been hearing from here.

So I want to thank you again for allowing me to speak, and I am going to step back and let the other speakers take their turn. Thank you.

DR. CARGILL: Thank you.

Tracy Swan, Treatment Action Group.

MS. SWAN: Hello, everybody. Thank you for the opportunity to speak. I do not have a financial relationship with the sponsors or the competitors, nor did anyone pay for my travel other than the organization that I work for, which is a nonprofit.

I'm very excited about these drugs, the one we discussed yesterday and today. I think they

open up a lot of new opportunities. I do want to say, okay, a rash is a scary new territory for people who are used to thinking about a liver. But people have had years of experience with interferon, which is also pretty nasty, and I feel like it's really a question of partially the labeling, partially pictures and other things that make it easier for both patients and providers to assess the risks and benefits of how to use a drug and that education is going to continue to be extremely important.

So these are the key issues I'd like to talk about. Yesterday you saw the same grim scenario that patients face, and I'd like to say there's a lot of information on drug-drug interactions with telaprevir. There's a lot of information in people with -- or some information in people with hepatic and renal impairment.

I'm disappointed that studies for more desperately ill patients with really urgent need couldn't have begun a little earlier, given that Phase 3 started in 2008 for this drug. I'm also,

as has been mentioned, disappointed by the low enrollment of both populations among whom hepatitis C is highly prevalent and populations that really need more effective therapies.

There are some clinical issues. The long-term clinical implications of protease inhibitor drug resistance in hepatitis C are largely unknown. And instead of looking at what might be in someone's blood years after they stopped treatment, I think it would be quite helpful to apply the pressure of the drug again in the context of peg/ribavirin in people who are in early monotherapy studies and only got telaprevir who have a resistance to see what happens when they get retreated with standard of care. That's a really important way to get there.

There may be a possibility to use this drug twice a day. I know there are studies that are looking at that. It would be great to resolve that quickly because it's a lot easier to take drugs twice a day than three times a day.

Since the SVR rate among prior null

responders with cirrhosis is low -- these are people who are pretty desperate -- it would be great to have early predictors of response or nonresponse, or any additional information to help people guide their decision-making process about treatment.

Stopping rules, which hasn't come up yet, I think should be really explained clearly to patients and providers, especially in the absence of a treatment guidelines panel. And I hope that providers beware of drug-drug interactions, and we've heard a lot about the importance of rash management.

Quickly, I know that there was some talk about post-approval studies. In particular, cross-country multi-DAA trials in hard-to-treat populations would be great. I think there is pretty urgent unmet need, and we've already got proof of concept that this can work.

Thank you very much.

DR. CARGILL: Thank you.

Lorren Sandt, executive director, Caring

Ambassadors Program.

MS. SANDT: Good afternoon. Thank you for having me here today. Lorren Sandt with the Caring Ambassadors Program, Oregon City, Oregon, and I'm the chair of the National Viral Hepatitis Roundtable.

Thank you for your presentation today. I do want to say to the sponsors that that was a very clear, concise presentation, and really, really appreciated it. It showed the care that you put into that. Thank you.

I do have the same concerns that I had yesterday about adherence. A three-times-a-day drug at q8 hours with food with fat, while you're having diarrhea, nausea, and vomiting, and a little bit of brain fog to go along in there, I'm concerned about adherence. And so again I'm going to ask that the FDA use as strong language as possible about making sure that there are tools in place for people to actually have good adherence.

I also am concerned about the lack of providers who are going to want to pick up this

treatment. So, again, that's why I thank the sponsors for being so clear about the protocol because I think the clearer the protocol, the more doctors who are going to be willing to treat hepatitis patients. And we do have a lack of hepatitis doctors treating patients.

I don't know if the panel is aware, but many patients have to wait six months to see a hepatologist, and often they don't even get to see one unless they're in stage 3 or stage 4 fibrosis. So we're talking about the most difficult-to-treat patients, and we're holding back patients from treatment that really could be treated more successfully and with shorter duration if we had more doctors treating. So, again, the more clear and the more concise you can make the directions to physicians, I think we'll have more physicians treating.

I do understand that some drug-drug interaction studies are going to be taking place with milk thistle, so I'm not going to make that comment today. But I think all alternative

medicines that are common, such as St. John's wort and milk thistle, need to be studied, and that also needs to be in the label so that the 40 to 70 percent of patients who are taking those herbal therapies are understanding what kind of implications it can have if they continue to take those while they're on these treatments.

Other than that, I just would like to say that I do endorse the approval of both of these products. Yesterday you voted for one, but really looking forward to seeing more options for patients, and seeing those hundreds of thousands of people that are treatment-experienced cured, and also getting those people, those millions of people, that are undiagnosed cured.

Thank you very much.

DR. CARGILL: Thank you.

Michael Ninburg?

MR. NINBURG: Good afternoon. Thank you for having me back here this afternoon. My name is Michael Ninburg. I am the executive director of the Hepatitis Education Project in Seattle,

Washington. Our organization has received support from the sponsor, and I do have experience with a product of the sponsor. I was a patient in one of the sponsor's Phase 3 trials.

I'll make my comments brief today. I was very encouraged by the unanimous vote yesterday to recommend approval of boceprevir, and I fully expect the same today. Choice is good for patients, and as was mentioned earlier, this is indeed a watershed moment in the history of treating hepatitis C.

A couple of things that I would like to say. Again, the treatment is not going to be easy. It's going to become a much more complex regimen. We heard today about mitigating side effects. Dr. Korman mentioned the fact that those who are treating hepatitis patients are not dermatologists.

I was very encouraged to see from the sponsor the plans for provider and patient education. That's going to be absolutely crucial. Adherence to therapy and mitigation of side effects is going to be the only way that patients are going

to have the best chance that they can of getting cured.

I will end on the importance of getting these drugs and new drugs that are in development to those who most need them. And this will be more for the folks at FDA, but if we could get a bit of a push for an expanded or early access program for those who are most at risk of decompensating and getting to some of the more serious sequelae of this disease, that would be something that will save lives.

Thank you.

DR. CARGILL: Thank you.

Jules Levin?

MR. LEVIN: Let me try and be brief. I have six things I want to mention.

First, it's been mentioned a couple of times already, the rash. I'm concerned about the rash, and so the education for clinicians and patients are really crucial here with regards to the rash. And I just want to give two examples of my concerns about the rash.

One, what happens if a patient, who knows nothing about rash -- because I think the rash is new to this field of hepatitis; we're all trying to understand it better. So what if a patient gets a rash on a weekend? What are they going to do? If they get nervous, they may stop telaprevir without knowing that they probably could have waited till Monday to go see their doctor.

Let's just say that their clinician that they go see on Monday is not adequately knowledgeable about the rash. It's one thing if you're going to see Ira Jacobson at Cornell and he sends you up to 3 to see dermatology. What if you're in some small clinic in some far reaches of Los Angeles or New York or somewhere, and they don't have a dermatology clinic to send you to? So how about educating all these potential clinicians or prescription writers about this?

Now, I understand that -- I'm sure Vertex is thinking about this and understands it. But I think thinking about it and being successful at it are two different things. So rolling out an

adequate education program for patients and clinicians is really crucial.

I want to mention -- early access has been mentioned. I think this needs to be expanded on. We're talking about people who have advanced disease, who have not decompensated yet, but people who have advanced compensated cirrhosis.

We really need a study, not access, not expanded access in the mold of HIV, but a well-controlled, monitored study where adequate PK has been done previously. And these patients need two or more oral therapies with or without peg/ribavirin because, obviously, most of them have already been through peg/ribavirin, so they're going to need at least two orals.

That's what we're talking about, and the FDA had a hearing about this last year. And I haven't heard enough from the companies in terms of addressing this and planning studies. So if the companies are planning studies to address this, and if FDA is supportive of this -- because I'm not convinced that they are -- I'd like to hear about

this, that this is in the plans, we're thinking about it, and we're planning this.

I want to mention also the issue of -- so I think that I support the indication for null responders here today, the 33 percent. I think the prospective data supports that. And one reason I think I support the indication is because without an indication, we may not get payers behind it for all the patients that do need it.

But we do need adequate education because some patients can wait and some patients may not be able to wait. So I think we need to explain this, so not every null responder needs to go on therapy; they can make a thoughtful decision about whether to use the drug or to wait.

I want to talk about resistance for a minute. So I think it was clear today in the presentations that with clonal sequencing, resistance seems to go down. But even in the FDA presentation, the 155K after 36 months was still there in 3 percent of patients. And so the conclusion from both Vertex and the FDA was, we

don't know what this means clinically. But what I'm worried about is that outside of this room, at conferences and other places, you hear thought leaders say, we can retreat patients successfully with protease inhibitors.

I'd to put a stop to that. I'd like a more thoughtful discussion about that to go on, that we really don't know the answer. One of the answers would be to try and design, perhaps, a retreatment study that would be ethical for patients.

So I guess lastly I just want to say patient support services. You know, in HIV we have the Ryan White Care Act, and we have nothing like that in hepatitis C, and I don't think that there's anything going to happen in the near future.

So I'm very worried about it because, as has been mentioned by some of the speakers here, and we all know, these treatments are going to be very complicated, and there are no real support services for patients. Maybe in some of the major clinics, like at Cornell or Mt. Sinai in New York, they have some supportive services. But outside of that,

there's very little patient support services.

I don't know what the FDA can do about this, but I just wanted to mention that today because there are companies here today, and the companies are going to have to pick up the slack here to try and provide this because there's very little government support at this point.

Thank you.

DR. CARGILL: Thank you.

Colin Schwartz?

MR. SCHWARTZ: Good afternoon. My name is Colin Schwartz. I am with the National Alliance of State and Territorial AIDS Directors, or NASTAD. NASTAD represents the health departments, HIV directors, and the viral hepatitis coordinators. NASTAD does receive funding from Vertex but did not support my travel. Yesterday you heard from my colleague, and I have similar remarks today.

While not necessarily in the purview of the Antiviral Drugs Advisory Committee or the FDA, I would like to use my time today to urge my colleagues in the room to consider some overarching

comments, overarching issues with this new, important drug.

Specifically, I would like to remind all of us that given the lack of public health infrastructure for viral hepatitis and the many barriers to care for persons living with chronic hepatitis C, a cure for hepatitis C is not enough unless we do two things.

First, a cure must be affordable and its coverage comprehensive. The cost for this new treatment will be added onto the current standard of care. Further, we need a robust patient assistance program that provides affordable coverage for ancillary costs such as PCR, liver biopsies and liver tests, management of treatment side effects, and counseling and risk reduction services, especially for those who are uninsured or underinsured and are hard to reach by the healthcare system or do not readily access the healthcare system, even under health reform. We recommend that such a patient assistance program target these populations.

Second, a cure must rely on infrastructure, with the government and the industry's support, to increase funding for screening and testing, increase staff capacity in medical settings, and increase the number of educated health providers in order to identify those who need treatment in the first place.

In order for this new treatment to work, new diagnoses are required. Unfortunately, 75 percent of Americans living with chronic hepatitis C do not know it, or roughly 3 million. The Institute of Medicine recently reported a lack of knowledge and capacity among providers to identify infection and deliver expert care and a lack of knowledge among the public, most importantly, among populations at risk.

Even with this new treatment, low provider awareness will continue to lead to lower than anticipated utilization of this drug and misdiagnoses. And we all know the numbers of specialists, such as infectious disease doctors, hepatologists, and gastroenterologists, are

limited. Further, low public awareness will continue to lead to misinformation and missed opportunities for prevention and treatments.

I would like to close by saying it behooves all of us to work together -- industry, the community, and the federal government, which is coming out with its first-ever viral hepatitis action plan in two weeks from today -- and to work quickly, because if we do not, we will not capture the 75 percent of those who are living unknowingly with hepatitis C.

We will not prevent the costs associated with liver cancer caused by hepatitis and the care and treatment of persons living with chronic hepatitis, which is estimated to increase by over 85 billion by 2024. And we will not prevent progression to liver disease and liver cancer among the estimated 4 million people living with HCV.

CDC's Division of Viral Hepatitis has said that if we have the capacity in this country to effectively combat this epidemic, we could increase diagnosis rates from 30 to 40 percent up to 75 to

80 percent, avert 227,000 cases of end-stage liver disease and 11,000 liver transplants, and reduce new infections by 50 percent by 2020.

All of these estimates were made presumably based on the current standard of care. Think of what we then could accomplish if we invested in public health infrastructure with this new cure. Thank you.

DR. CARGILL: Thank you for your comments.

Paul Brayshaw?

MR. BRAYSHAW: Good afternoon. My name is Paul Brayshaw, and I'm here on behalf of people with bleeding disorders. And I have no conflicts to report, although I have to say I am conflicted. Among people with bleeding disorders, there's a crisis. Without access to therapy, so many of the people that are affected are going to either face a liver transplant or die. We've had these illnesses, hepatitis C for a long time, but we're also confronted by HIV and other comorbidities.

So we salute the FDA for the early approval or the potential approval for telaprevir and

boceprevir, but we do seek other urgent developments to access new and far better treatment options.

As I mentioned the other day, nearly the entire cohort of people with hemophilia over 30 are infected or were exposed to hepatitis C. As a result, we have a long-term illness, upwards of 30 years. Because of the problems with bleeding or our ability to stop bleeding, those issues could be further exacerbated by the products being considered, as well as hepatitis C or HIV medications and HIV in and of itself.

We would like to encourage the FDA to support advertising or to support advertising and educational materials that indicates difficult-to-treat populations for people who might have these types of bleeding issues, with adequate warnings indicating the treatments that could potentially lead down this road.

One other issue I mentioned the other day, too, is that we want the FDA to recognize the cost of therapies for hemophilia and other

comorbidities. On average, hemophilia costs 100- to $150,000 a year. So that cost, plus the other costs associated with the treatments for hepatitis C, could potentially cause some adherence issues or access to therapy issues.

So our lives basically depend on access to these therapies, and we hope that the ability to -- the information available for treaters is going to allow us appropriate access.

Finally, I just want to say that we appreciate the guidance and support of the FDA in pursuing small group trials, and we just would like to find additional -- or we seek additional efforts to provide that further guidance so we can get access to those trials within small groups or other difficult-to-treat populations.

Thank you.

DR. CARGILL: Thank you for your comments.

Sonia Spangenberg?

MS. SPANGENBERG: Hello. I'm here just on my own behalf as a telaprevir trial patient, and also as a R.N. who has cared for, in ICU

environment, patients with end-stage chronic liver disease and liver transplants.

When my husband and I were diagnosed in 2008, it was really very devastating because I knew the potentials of this disease. When I started researching clinical trials and I came across telaprevir, what I read -- at this point they were doing stage 3 trials -- gave me incredible hope. And what I've seen as far as the outcomes from the stage 3 has been just reinforcing everything that I had read.

What I experienced during the trials, I experienced every single one of the side effects that were mentioned today. I did have the skin rash reaction, and I ended up having to stop telaprevir at week 7. My husband and I were both early responders and we both have maintained SVR, and I am very grateful for having had the opportunity to be able to try this drug.

I do have serious concerns about how the providers out in the real world are going to use the information that you have in regards to

observing signs of the development of the skin reaction and progression of the skin reaction.

It is a little bit vague, and it can become very serious in a small percentage of the people. And because it's such a small percentage, I think it has the potential for kind of getting overlooked, and somebody might fall through the cracks.

So I would really like to encourage more development of more precise identifying protocols and treatment protocols and really look at how that's going to translate out in the real world because I've worked in the hospital environment, doctor's office environment, a clinic environment. I know the reality of the time that these providers have to learn about this information, much less do the assessments.

So, obviously, we also need to educate patients. We need to provide more pictures, I think, that would clarify. And that was just an overwhelming sense that I got from everybody so far today that it's just a little too vague. And so

that's the one thing.

Otherwise, I heartily endorse this drug approval. I think it's just too beneficial to snag up on something like that. And I think that's it. I had no financial strings, by the way.

DR. CARGILL: Thank you for your comments.

Michael Casey?

MR. CASEY: Hi. My name is Mike Casey. I have no financial relationship with Vertex. I'm just here on my own.

I was a patient in a phase 3 trial with telaprevir, and I had a sustained response. I had been under four different treatments before, had failed every one by week 12. And I have type 1A with cirrhosis, and I had given up hope.

I'm at gratitude to Vertex for offering a trial to me. And Dr. Younossi at Fairfax Hospital, I couldn't be happier. Thank you very much.

DR. CARGILL: Thank you so much for your comments.

KellyAnn Mann Hester?

MS. HESTER: Good afternoon. I want to

thank you for this opportunity to speak with the panel. And I have no financial disclosure, but I was a patient on Phase 3 of the null responders.

I'm the mother of four children and the grandmother of five, and so, obviously, on December 12th of 2009 when I had my hepatitis C fully relapse, obviously fully responding, I was excited and very scared. But I would like to go back to the years when I did all the different treatments that came along.

I was diagnosed in November of 1993. A well-meaning physician at the time told me I would not see my son graduate from high school. He had just started kindergarten. I walked out of that doctor's office that day and told my family that wasn't an option, obviously, and made up my mind on that day that I would have to try every treatment that came down the system for hepatitis C so that I could be with my child to see him graduate from high school.

Being a relapser is a very difficult situation. I have done every type of -- when I was

diagnosed in 1993, it was still non-A, non-B for most physicians, and there was no treatment. I've done interferon, interferon with ribavirin, pegylated interferon with ribavirin at half strength, pegylated interferon with ribavirin at full strength, and now with the telaprevir. Telaprevir gave me the clear. I have no reason to think that the telaprevir wasn't the answer.

I did get the telaprevir rash. I had it on my hands, my legs, and my feet. But it was very little consequence to me, and would it have made a difference if you were telling me it would save my life? Absolutely not. I would do everything in my power to save my life.

My physicians played a huge role in my ability to get treatment and be treated because two physicians had to step aside and say, you need to go to somebody else. You need to go be in this study, for me to get the treatment that made me so that I am virus-free at this moment.

I'm not even sure that I can explain to you that this saved my life. I think I was on a path

that was going to lead me to a place that -- I was in a place where I was living to die. I knew that -- or in my mind had thought this was going to be the thing that would take me. And I had already accomplished my goal, which was to see my son not only graduate from high school but from college. And so I had no hope left, that I thought I was going to live with this disease to die.

Now I'm living until I die, which is a whole new concept for me, because now I have many windows and many avenues available to me that I did not have before. So I wholeheartedly am asking you to please approve this drug for the general public so that other people can tell my story at some point in time.

I thank you very much.

DR. CARGILL: Thank you for your comments.

DR. BIRNKRANT: I thought before we would go to the questions that it would be helpful for the panel or the committee if Vertex would present their rash management plan that was used in the clinical trials to help answer some questions that

it seems as though the panel still has.

DR. KAUFFMAN: Yes. Thank you, Dr. Birnkrant.

Just following up on some of the discussion right prior to lunch, I'm actually going to ask Dr. Stern to come up to provide some comments related to the severe cutaneous adverse reactions that were being discussed at that time. Then we will show the rash management plan and discuss that for the committee. Thank you.

DR. STERN: Thank you. I'm Robert Stern. I'm at the Beth Israel Deaconess Medical Center and Harvard Medical School. I was the head of the dermatologic evaluation panel for Vertex, and I'm here today as a consultant to them.

So first I think it might be useful for me to describe a little bit of our activities. There are three of us, Jean Claude Roujeau, Maja Mockenhaupt, and myself, who reviewed a total of 221 cases of rash. And those were all materials, including photographs on approximately two-thirds of those cases that were either of particular

interest or led to stopping of any of the medications. Our review, in addition to photographs, included biopsy specimens when available, which was in about 50 percent of eruptions that were in Phase 3 that ended in -- that led to discontinuation, and also the clinical records in terms of laboratory studies, dermatologic examinations.

At the time of review, we were blinded in any of the blinded studies as to whether patients were on triple therapy or receiving placebo plus peginterferon and ribavirin.

We reviewed the materials separately, came to our separate conclusions about extent, morphology, the extent to which it might in fact represent a SCAR, that is, Stevens-Johnson, TEN, or DRESS, drug rash with eosinophilia and systemic symptoms. And then periodically, the three of us came together and came to consensus. And I would say that in the great majority of times, there was a high degree of agreement even before we discussed consensus.

In order to be able to give some idea of the likelihood of reactions, we used two separate standard algorithms that are used in case control studies, one for SJS and TEN and the other for DRESS, with "definite" meaning extremely likely that it was a case, "probable" meaning more likely than not, "possible" meaning not very likely to be a case but one could not exclude it. And we tried to be as sensitive as possible at the cost of specificity.

So with respect to Stevens-Johnson syndrome, there were three cases that rose to the level of any suspicion, one which we believed was a definite case. And this was a gentleman who was then 11 weeks past using telaprevir and had just started a drug between 1 and 2 weeks before that has been at least associated in the literature with causing Stevens-Johnson syndrome.

The second was a case we thought to be probably Stevens-Johnson syndrome, more likely than not, and that was a person on triple therapy in the relevant time window. The third was a possible

case, not very likely, but we could not exclude that possibility, also on triple therapy.

With DRESS, it's a great deal more difficult because, as Dr. Bigby pointed out, 50 percent -- in general, when you think of DRESS, you think of someone having 50 percent of their cutaneous surface covered with rash. And in fact, relatively few people had that. But we looked at anyone with extensive eruptions or any eruption and looked for eosinophilia and fever.

Absolute eosinophilia was rare, and because of the leukopenia, we decided to use a more sensitive criteria, which is percent eosinophils, and seeing if there was a substantial change from baseline, even though, to my recollection, none or at most one of these people had absolute eosinophilia at the time.

All of our DRESS cases had eosinophilia and fever. But in fact, by our criteria, there was one definite and two probable cases, which I think one should look at as highly likely to be cases. And there was the question of diagnosis at the site.

Two of the three had been listed as DRESS at the site, and one was just listed as rash at the site that we detected. There was one case of DRESS that the investigators indicated was such that we in fact excluded based on our review.

So I think if you want to put this into clinical perspective in terms of severe cutaneous adverse reactions, I think if I were thinking of this, particularly with Stevens-Johnson, I would think it is likely that this drug will have a risk profile not unlike that of Bactrim.

DR. KAUFFMAN: Thank you.

So I wonder if I could bring up the rash management slide. And, Dr. Singhal, do you want to talk about that? Thank you.

While it's coming up, I should just make a point. One of the comments from the committee earlier was that hepatologists and others taking care of patients with hepatitis C are not exquisitely knowledgeable in dermatology. When we designed the rash management plan, we took that into account, and we did not -- we wanted a plan

that would be practical for people who were not exquisitely knowledgeable in dermatology to be able to use.

Whether or not the correct dermatologic diagnosis is made, the plan provides an algorithm for stopping treatment that can be followed by anyone based on the skin area, whether or not a label of DRESS or just an eczematous rash or whatever else is put on it.

That's what we mean by being practical and manageable, in that anyone can use it. You don't have to have a specific dermatologic diagnosis. The criteria for stopping are directly in the plan, as you'll see. So if we can bring that up.

DR. SINGHAL: Thank you.

If you could put CS-16 up? So whilst it's coming up, I'm going to take you back to my core safety presentation, where I spoke about the rash management program within the Phase 3 program. I want to start off by saying that it's a very simple approach, and investigators were able to follow it. I do appreciate the comments that were made today

by the patient advocates as well as the committee, and please stop me if there are any questions at any time.

The first point that we were very clear about was that general principles for rash management should be followed. We also required monitoring for all rash events. What did this exactly mean? It meant that patients were to be told that the rash was possible -- informed consent had this information very clearly stated -- as well as physicians were made very much aware that a rash was possible.

They were also made aware of the fact that more often than not, they would be mild or moderate, but that all rash events needed to be monitored for the possibility of progression, which, albeit small, it definitely existed.

In addition, we provided a very simple algorithm where we said that if it was a mild or moderate rash, no study drug discontinuation was required. If it was a severe rash -- and we provided descriptions of each of these, so a mild

or moderate rash was either a localized rash or a rash that involved less than 50 percent of the body surface area, and while it may be disturbing, didn't keep the patient up at night or was not associated with extensive symptoms. That did not require any discontinuation.

Moving on to the description of a severe rash, I'd like to spend a minute here because this is really broken up into the two categories that I spoke of earlier, which I think have been raised as very specific points today.

One is a severe rash that involves an extensive body surface area and could keep the patient up at night, maybe associated with extensive pruritus, but in general is not a life-threatening reaction such as Stevens-Johnson syndrome or DRESS, as Dr. Stern just described. So, in a sense, it didn't have any mucosal involvement or it didn't have any lesions that may look like target lesions. That type of severe rash just required telaprevir to be discontinued.

Physicians were given more guidance on this,

where we asked them to monitor these patients very closely, and if they felt within 7 days that the rash had not abated after stopping telaprevir, they could think about stopping ribavirin and/or peginterferon. So that was the instruction for severe rash.

Rare severe skin reactions, which are actually included in the label for peginterferon and ribavirin, certainly were the ones that would require all study drug discontinuation and all medication discontinuation, because there are several drugs that can cause these reactions.

So that was, in essence, the rash management plan within the Phase 3 program. Within the Phase 3 program, we also built in within the rash management plan an extensive data collection plan. And that is exactly what you have heard from Dr. Stern with regards to the materials that were evaluated because we wanted to evaluate the severe reactions as well as the severe rash very comprehensively.

So I'd like to stop there. That was the

rash management plan in Phase 3. And the purpose of today is to translate this into the real world, which we realize and are committed to entirely.

So I'd like to put up RM-15, please. This is a very high-level management approach for what we are thinking about and planning for rash management within the real world and hopefully after the drug is approved. So the first would be very specific language in the label. This would be warnings for severe rash, but also, most importantly, to distinguish the severe rash from the severe cutaneous adverse reactions, and also to provide the information on the mild and moderate rash and alert prescribers to monitoring. We would also provide all the rates that have been observed during the Phase 3 program, and comparative rates with placebo.

The second point, which cannot be overstated here, is a very robust communication plan to patients and healthcare providers. And how are we going to do this? It's going to be a very robust medical education program. For patients, we are

going to inform patients that they need to connect with their healthcare providers, that I think a point was raised a few minutes ago about discontinuing. This is a very specific point that we will be stressing in education and all materials that are being prepared. They should not discontinue telaprevir on their own.

Healthcare providers similarly will know when to connect with their patients and what to look for, and to follow a very simple plan which says that if it's severe or you see any of these reactions, discontinue telaprevir.

In addition, to provide additional resources and support, we are preparing for a nurse hotline so that there will be the resource for physicians and prescribers who may not be familiar or may not be comfortable treating rash on their own.

Finally, I want to stress the point of medical education, which is going to be performed through multiple forums. And this is going to be via continuing medical education, our medical-to-medical-science liaisons, the field force, and a

lot of resources for patients and physicians which are going to help to communicate -- help patients and physicians and healthcare providers connect with each other.

So that's, in essence, the translation of the rash management plan from Phase 3 into the post-approval setting. And I'm happy to address any questions.

Questions from Committee to Sponsor and FDA

DR. CARGILL: Thank you.

I think at this point I would like, in the interest of time, for the committee to return to the questions they have for both the sponsor and to the FDA. And I will continue to take those names in sequence.

Dr. Giordano?

DR. GIORDANO: My question was addressed last session.

DR. CARGILL: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: Yes. In the briefing document, the sponsor indicated that virologic

outcome was assessed in what seemed to me quite a wide visit window. For subjects who had a treatment duration of 24 weeks, the visit window was week 32 to week 78; and for subjects assigned to 48 weeks of treatment, it was week 56 to week 78.

I'm not sure I'm understanding this. But I just wanted to make sure that it couldn't be the case that some people waited much longer than others to have their viral load assessed, and if that wasn't balanced on the treatment arms, there could be a bias, and that some people were looked at, at a much longer time after they had treatment than others.

DR. KAUFFMAN: Yes. So patients did come back at specific times to have their HCV RNA assessed, as we indicated. And we actually had very, very good adherence with that schedule. There was very little missing data. And we continued to follow patients out to week 72, even those who had stopped treatment at week 24 in the short duration arm so that we had common assessment

points in the protocol for everyone for their HCV RNA, and we had very, very good ascertainment out to week 72.

The way the analysis was done was that the last visit in that window was the one that was generally used for the adjudication of detectable or undetectable for the assessment of SVR. And the windows obviously varied depending on whether patients had stopped at 24 weeks or 48 weeks.

DR. ELLENBERG: And can you say anything about the comparison of the average window time on the treatment arms? It sounds like the time of what you used in the analysis varied. It was the last one. So for one subject, it might have been 72 weeks and for another subject it might have been 58 weeks.

DR. KAUFFMAN: Yes. But in general, the assessments were really done really very close to the nominal time that they were supposed to have come in.

I can ask Dr. Sankoh to come up and expand on that further, if you like.

DR. SANKOH: Hi. A.J. Sankoh, Vertex Biometrics. Yes. As Dr. Kauffman indicated, we actually have a common assessment for all the subjects. We realized that, yes, as you were saying, for those who stopped treatment at 24, compared to those who stopped treatment at 48, the duration of antiviral follow-up was different.

So we followed everybody to week 72. Even for those who stopped treatment earlier, they're not finished, they're assigned treatment regimen. And there was a very small loss to follow-up of all subjects, less than 1 percent, actually, in all the treatment groups. So the assessment was really intentionally done that way to make sure we have consistency in the way we assess.

DR. ELLENBERG: Okay. So the way I'm reading it I think then is incorrect. You're telling me that almost everybody on all the arms were in fact assessed at approximately the same time?

DR. SANKOH: Yes. Yes.

DR. ELLENBERG: Thank you.

DR. CARGILL: Thank you.

Ms. Young?

MS. YOUNG: Yes. I was wondering if the sponsor could summarize the protocol for anemia management. Is it a very clear-cut protocol that is going to be easy to understand and follow? Thank you.

DR. KAUFFMAN: Yes. As I mentioned, it was primarily based on the ribavirin package insert. I'll ask Dr. Singhal to come up and talk about that.

DR. SINGHAL: Here again, I'd like to go back to my safety presentation. CS-26, please.

Anemia management was included in the protocol very specifically, and it required prescribers to follow the ribavirin dose modification per the ribavirin label. However, because we were aware from the early Phase 2 data that telaprevir can cause an additional gram or 1.5-gram decrease, we did specifically mention that telaprevir discontinuation could be considered per clinical judgment, and investigators were aware of

this based on their data that was included in the investigator brochure in the guidance to the investigator section. However, we pointed out that telaprevir could not be reduced and restarted, just like for rash.

Discontinuation. If the investigator followed the ribavirin label, which led them to discontinue ribavirin, they needed to also discontinue telaprevir because we were aware that telaprevir could potentiate the anemia, and we did not want patients to continue if the anemia had gotten to 8.5 or lower, where ribavirin needed to be discontinued. So we wanted to take a conservative approach. And that was, in essence, the management. Monitoring was done at regularly scheduled visits for hemoglobin.

Here again, maybe if I could translate this on, to what is going to happen beyond the Phase 3 program and how we are going to build on this for the future.

If I may have that?

DR. CARGILL: If you can be succinct.

DR. SINGHAL: Yes. Sure. Please, can I have RM-33?

It's again going to be a three-pronged approach, with the labeling very specifically giving the information on anemia, alerts to monitoring hemoglobin, providing the details of what is the pattern of hemoglobin decrease and recovery, as well as the details of what was the use of ESA during the clinical trial program -- because it is not an FDA-approved drug for hepatitis C-related anemia -- and ribavirin dose modification.

In addition, we'll be reaching out to patients, healthcare providers, with the same information, very much like the rash, with the alerts to monitor and also to use clinical judgment and discontinue per the same algorithm. And medical education, the nurse hotline, the websites available with this information, and reach-out programs will be identical, just like us.

DR. KAUFFMAN: Thank you.

DR. CARGILL: Dr. Clay?

DR. CLAY: Put your slide back up because I guess I have a practical question.

We have two drugs that are going to be used to treat hepatitis C, pegylated interferon and ribavirin. We now have a choice, potentially, of what the third drug will be. Both of these third drugs have shown that they can cause anemia.

Historically, when a person developed anemia during the course of therapy for hep C, you reduce the ribavirin, potentially interrupt therapy. You have made it very clear if you interrupt ribavirin you must also stop telaprevir.

Dr. Friedman is seeing somebody in clinic. His patient has shown up with anemia. How can he tell if the anemia is from ribavirin or is it from telaprevir? Because we can discontinue our telaprevir and perhaps switch to another drug that has been shown to be effective in combination with pegylated interferon and ribavirin.

My question specifically gets to, can you tell me what exactly the anemia looks like with respect to telaprevir? Can we distinguish the

anemia of telaprevir from the anemia of ribavirin? Because it directly affects how we're going to manage the person in front of us.

DR. KAUFFMAN: So I guess I'd answer that by saying that the hemoglobin drops that are seen --

DR. CLAY: What I'm talking about here is sideroblastic anemia with erythroid hyperplasia, vacuolization of erythrocytes, increased serum iron concentrations.

Do you have that information that a clinician could then look and say, "Oh, gee, that's not present, so it must be from the ribavirin. But, oh, wait, that is present, so let's switch over and let's use perhaps the other third drug"?

DR. KAUFFMAN: Yes. So I guess I have to answer that question by saying that, of course, because both telaprevir and ribavirin are obligatorily given together, and whatever anemia occurs is an anemia related to the regimen, the data that we have in our program really cannot answer the question as to which specific component is related to the anemia in any given patient.

All we can say is that on average, there's a 1- to 1 and a half gram further drop in hemoglobin as compared to peg and ribavirin alone, and that it can be managed by ribavirin dose reduction.

DR. CLAY: And you had --

DR. KAUFFMAN: I understand your point, but we have -- I have no data.

DR. CLAY: You had zero occurrence, zero change in hemoglobin in your normal, healthy studies when you administered it for 12 weeks? So that's kind of the life cycle of the red blood cell.

DR. KAUFFMAN: No healthy volunteers received the drug for that long. And all healthy volunteer studies are confounded a little bit by the amount of blood drawing that occurs in clin pharm studies, and so they're almost always drops --

DR. CLAY: Yes. You know what? You pay them enough, they'll get it drawn.

DR. KAUFFMAN: Pardon me?

DR. CLAY: You pay them enough, they'll take

that blood.

Okay. So you don't have that information?

DR. KAUFFMAN: We do not.

DR. CLAY: We cannot tell what's causing it, so we don't know if it's going to be safe to switch someone from telaprevir to another third drug. Are we going to have to --

DR. KAUFFMAN: We simply don't have that information at this point.

DR. CLAY: Okay. I do have a second question.

DR. BIRNKRANT: That's been brought up twice now, about switching from one to another. But there's no data with regards to that.

DR. CLAY: I was proposing a hypothetical, that in the future, if there is a third agent, we would like to know which one is causing the anemia.

DR. BIRNKRANT: Right. But that I think would require additional data, which we don't have at this point.

DR. CARGILL: Dr. Roland? Dr. Ghany?

DR. GHANY: Yes. Thank you.

So I wanted to get back to the issue of a ribavirin dose reduction. And either the FDA or the sponsor could explain to me the quantity of ribavirin dose reduction that we've been talking about. Is this 200? 400? 600? And the timing of the reduction, and then how many individuals restarted back at their prior dose? So what was the average ribavirin dose in the first 12 weeks during triple therapy?

DR. KAUFFMAN: So the dose reduction that was recommended and what is in the ribavirin package insert is to reduce the dose in half. It depends on what weight the patient is and which dose they're taking. But the initial dose reduction is in half. And then if there's a failure of response, the subsequent reduction then is to discontinue ribavirin, and that is what was followed.

We understand in the community there are many ways that ribavirin is being managed. But in the protocol, we had to stick with the dose reduction scheme that was actually in the ribavirin

labeling.

DR. GHANY: So do we actually know what the average ribavirin dose was in the first 12 weeks?

DR. KAUFFMAN: I don't have that information offhand. I can see if we can get that, but I don't know that.

DR. GHANY: Okay. And I do have a second question, if I may, and it pertains to the design of study 111. I think that's ILLUMINATE.

DR. KAUFFMAN: Yes.

DR. GHANY: I wondered, why did the randomization occur at week 20? And was that because some individuals, after telaprevir was discontinued at week 12, did they have virological relapse? And if so, were those patients excluded from the analysis? How was that handled?

DR. KAUFFMAN: Yes, you're correct. The randomization took place at week 20. If you remember, the study was really designed for a very specific purpose, and that was really to examine whether there was any benefit to extending treatment to 48 weeks compared to 24 weeks in those

who had a rapid virus -- an eRVR.

Therefore, we wanted to maximize the SVR rates in those randomized arms to reduce any noise that might occur by discontinuations and other things. So we randomized relatively late in the treatment period.

We certainly accounted for every patient who entered the trial. The overall SVR rate of 74 percent that we showed includes everyone, no matter what happened to them, whether they're randomized, not randomized, assigned to 48 weeks, or had dropped out prior to that. Everyone was accounted for at the end of the study, and that's the 74 percent SVR rate.

Of course, in those who discontinued earlier, if you have the study design in mind, you remember that lower arrow. Those patients, of course, because they discontinued early for any number of reasons, had a lower SVR rate than those who didn't. Everyone was accounted for in the end. That's why we presented that overall rate, to give you an idea of sort of what the overall outcome was

in the entire trial.

DR. GHANY: But patients between week 12 -- dropouts between week 12 and 20 were not counted in the rates, the final rates, at 24 and 48. Is that correct?

DR. KAUFFMAN: Those who dropped out between week 12 and 20 were not randomized. They are accounted for in the analysis later, but they were not part of the randomized group. Patients had to be on treatment at the time of randomization in order to be randomized.

DR. GHANY: And do we know what that number was?

DR. KAUFFMAN: The number who dropped out?

DR. GHANY: Yes, between week 12 and 20.

DR. KAUFFMAN: It was about 5 percent. The eRVR rate in the study was 65 percent, and about 60 percent of patients were randomized. It was about 5 percent who didn't make it from week 12 to week 20.

DR. GHANY: Thank you.

DR. CARGILL: Thank you. I'm going to ask

the panel to be mindful of our time so that our questions can be succinct.

Dr. Knodell?

DR. KNODELL: Just one quick comment and then my question. My comment is that the cirrhotic patient population are the people that most need your treatment. Relapsers responded really quite well to treatment, but we know that they're pretty easy to treat anyway.

I'm wondering whether perhaps some additional studies with telaprevir might be worthwhile at a higher dose and that perhaps the poor results in cirrhotics were due to low drug bioavailability.

My question relates to one that I'm surprised hasn't been raised before, and that's to the information. You haven't provided as much information on drug-drug interactions. You gave us an intriguing slide, CO-5, that said a bunch of studies had been performed, and in the information you provided to us pre-meeting there was a statement that methadone concentrations dropped off

in people that were dual exposed to telaprevir.

Can you comment more on your drug-drug interaction studies? I'm sure you've got that information.

DR. KAUFFMAN: Did you have a specific study in mind? Would you like to see the -- you mentioned methadone. Is that one you'd like to see? Otherwise, there are a large number of studies. We can certainly go through them. But if there are specific ones you're interested in, we can focus on those.

DR. KNODELL: Well, I don't know that the committee needs to see everything. But, yes, I mean, methadone is -- certainly in the VA, it's a commonly used drug in hepatitis C patients. Pick a couple that are most likely to be used concomitantly with patients with hepatitis C.

DR. KAUFFMAN: Fine. So I'll ask Dr. Garg to come up and talk to you about the methadone interaction study.

DR. GARG: So if I could have slide DI-38. While the slide is being put up, I would just like

to tell you about the design of the study.

This was a study done in healthy subjects -- well, non-HCV subjects who were on methadone for a few weeks, at least. I think it was more than a couple of months. And they were stabilized -- and they were on an individualized stable dose of methadone. And then their PK levels of methadone were taken before starting telaprevir as well as after starting telaprevir.

This slide shows that -- in the green is the individualized methadone and the red is the individualized therapy of methadone with telaprevir. As you can see, there's about a 30 percent drop in the AUC of methadone. This is for the total drug, however.

We actually examined the unbound levels of methadone because we thought that they might be approaching binding displacement, and we actually found that the unbound levels of methadone were actually similar. So it also accounted for the fact that there was no increased withdrawal symptoms in the subjects that had a lower level of

methadone.

So we believe that this interaction was actually not clinically significant because the protein binding displacement reduces the total levels of methadone but not the unbound levels.

DR. KNODELL: Do you have anything on midazolam?

DR. GARG: So in the case of midazolam, we studied, again, midazolam before starting telaprevir and then, at steady state of telaprevir, a single dose of midazolam, 2 milligrams orally as well as with IV midazolam. And for that, we found that oral midazolam levels were increased roughly about ninefold with telaprevir. So we concluded that telaprevir was a potent inhibitor of CYP3A based on that.

DR. CARGILL: Thank you.

Dr. Friedman?

DR. FRIEDMAN: My question is also to the sponsor, and it's about the rash management program. Will that include specific recommendations regarding the use of

antihistamines, topical and systemic glucocorticoids, and referral to a dermatologist?

DR. KAUFFMAN: I'll ask Dr. Singhal to come up and address that.

DR. SINGHAL: While the use of treatment used during the Phase 3 program was collected and we have this available, we are unable to assess whether they were effective because, as you know, 93 percent of subjects don't go on to progress. So we're not sure whether it was the treatment or they would have resolved on their own.

So we don't have -- we will not be including specific recommendations. However, good skin care practices will be included. And we will have a five-step approach where the first step will be, really, patient awareness. Clinical diagnosis will be step 2. Assessment of severity, management as per general principles of management, and we do believe that it is an eczematous rash for which, in general, topical steroids and good skin care practices do help to keep patients on.

I think one very important point is it's a

12-week duration, and it's the first 12 weeks. And we do know that the rash improves significantly as soon as telaprevir is stopped. So we do believe that once telaprevir is completed, with good skin care management, this will be really very manageable.

DR. FRIEDMAN: Thank you.

DR. CARGILL: Thank you.

Dr. Strader?

DR. STRADER: This is just a clarification question on the rash. I think it was Dr. Stern, if I have the name right, who presented the information on the severe, the Stevens-Johnson, the DRESS.

But my confusion is the use of the terms "definite," "probable," and "possible." Are you talking about the possibility that this was a rash or the possibility that it was associated with telaprevir? So there's a difference between those, if you understand what I mean.

DR. KAUFFMAN: It was definite, possible, or probable related to that specific diagnosis. It

had nothing to do with the relationship to the drug. Because most of them occurred in telaprevir, we considered that the relationship was certainly at least possible --

DR. STRADER: Possible.

DR. KAUFFMAN: -- related to telaprevir.

DR. STRADER: Okay. Thank you.

DR. CARGILL: Dr. Giordano?

DR. GIORDANO: We haven't heard anything about futility rules in any of these trials. It was brought up by the public comments. Were there any futility rules in these trials? And if not, were there any post hoc analyses that would suggest that there could be?

DR. KAUFFMAN: Yes. Each of the trials included stopping rules for virologic failure and also the typical quote unquote "futility rules" at weeks 12 and 24 that are generally applied for current standard of care for hepatitis C.

In the case of the treatment-naive studies, the virologic rule was those patients with an HCV RNA above 1000 international units per mL at week 4

were considered to have either incipient breakthrough or failure. And those patients were recommended to stop telaprevir, but they could continue peg and ribavirin. Those who had detectable HCV RNA at week 24 had to stop, as they are in the current rules.

In the treatment failure study, there were slightly different stopping rules. The threshold was somewhat lower. And this is something that we'll be working with the agency on to devise appropriate stopping rules for telaprevir.

We're obviously looking back now at the Phase 3 data to learn more about what the rules perhaps should be, and we'll be certainly interested in talking to them about what to include in the labeling.

I think the issue perhaps is most acute in the null responder group, where we know that virologic failure occurs most frequently, and we certainly will be looking at futility rules there to be able to identify patients early who have no chance of achieving an SVR, therefore preventing

them from being exposed to the regimen for the full length of time.

Obviously, we can identify many of those patients quite early on in treatment, and therefore, they don't have to be exposed to the drug for very long. And again, we'll be working on those rules with the FDA. We've had some preliminary discussions with them and will obviously continue after this meeting.

DR. CARGILL: Thank you.

Dr. Bigby?

DR. BIGBY: Actually, this is a point of clarification for the committee. I don't know, it's not really a question. So if you want to do it later, I can do it later.

DR. CARGILL: Okay. Then why don't we do that after the break.

Ms. Valbh?

MS. VALBH: During the FDA presentation, a comment was made that baseline hemoglobin was hard to assess. And so my question is, was it not collected in any of the trials? Was the baseline

hemoglobin not collected?

MR. FLEISCHER: No. It was clinical anemia. We have hemoglobins on everybody at multiple time points.

MS. VALBH: At multiple time points?

MR. FLEISCHER: That wasn't the issue, no.

MS. VALBH: And then for the sponsor, there's a lot of guidelines on how anemia should be managed and how often the labs should be done. But in clinical practice, it's a little grey. And even now with ribavirin, it's a bit grey, and especially for those clinicians who don't really treat hepatitis C patients that often. So they look mostly towards what was done during the clinical trials.

During all your clinical trials, how often was a CBC assessed? Was it every 2 weeks? Every 4 weeks? Once a month? Can you provide some clarification on that?

DR. KAUFFMAN: In the trials, certainly during the first 12 weeks, which was the period of telaprevir administration, patients were seen no

less often than every 2 weeks, and so we have very frequent hemoglobin measurements during that time.

Again, in thinking forward, we're looking at those data to try to determine what the most informative time points would be to make recommendations once the drug is approved, what the labeling should recommend in terms of monitoring. And, again, that's something I think that we in the FDA will deal with. But we're going to look back at our data to try to find the most appropriate time points for monitoring.

Since for eRVR status HCV RNA has to be assessed at week 4 and again at week 12, those are obvious points at which time we would look at them, but there likely will be points in between as well.

MS. VALBH: Okay. Thank you.

DR. CARGILL: Thank you.

Dr. Clay?

DR. CLAY: I'm going to go back to a point I raised much earlier in the day, and it relates to your pyrazinoic acid level concentration. That's part of your metabolite.

I understand that you performed some pharmacokinetic assessment during a phase 2 study that involved 17 individuals. My question relates to the fact that the more I look at the side effect profile of this, it really looks like pyrazinoic acid is causing a great deal of this.

The clinical implication of that is you did not perform PPD baseline on people at the start of the study. People who have hepatitis C are also the same population that are at high risk for tuberculosis. Obviously, we would be concerned if someone were to receive pyrazinoic acid by itself for the duration of period of hepatitis C therapy.

So I guess I need to see the pyrazinoic acid assay results. And if you could show me that -- because, granted, I don't know all there is out there, by all means. My children tell me that all the time. If you could tell me what assay you use because I didn't think there was an assay for pyrazinoic acid; that there was an assay for pyrazinamide, but pyrazinoic acid is measured through 24-hour urine collection of

5-hydroxypyrazinoic acid.

DR. KAUFFMAN: So I'll ask Dr. Garg to come up. I actually wanted to correct something that I told you earlier. It turns out that patients with tuberculosis were excluded from -- anyone with active tuberculosis would have been excluded from the trials.

DR. CLAY: I was a little surprised, yes. That's generally a standard enrollment criteria.

DR. KAUFFMAN: Yes. That's correct. So I'm sorry I misspoke at that point.

I'll ask Dr. Garg to come up to talk about pyrazinoic acid assay.

DR. CLAY: Thank you.

DR. GARG: So we did have a pyrazinoic acid assay, which was an LCMS assay. And we used the standard pyrazinoic acid as a reference standard for that.

There are at least two papers that I'm aware of -- And, actually, those are just the papers that I have -- which have pyrazinoic acid PK described in there. The maximum concentrations of pyrazinoic

acid in the plasma was reported from about 5.5 micrograms to 67 micrograms per mL. These were in healthy volunteers, subjects taking about 35 milligrams per kilograms of dose of pyrazinamide. And they measured both pyrazinamide and pyrazinoic acid in that. And the levels that we observed, the maximum levels that we observed, on an average was about .4 micrograms per mL.

So that's why I say it was about 14-fold to more than 150-fold greater in the subjects that took pyrazinamide as opposed to telaprevir at steady state of telaprevir.

DR. CARGILL: Thank you.

Dr. McGovern?

DR. MCGOVERN: I'd just like to ask some questions about the rash again.

In terms of the information you gave to us, you said that the median onset of rash was about 25 days, and about a third of those occurred in the first month. I just wanted to know, was there any information that drug rashes that ended up being severe, did they have a different tempo? If a rash

develops that's mild to moderate, was there a certain window of time that let's say that rash stayed mild to moderate, that severe rash didn't seem to occur?

I guess I'm just trying to think about this issue of monitoring closely how often, when can I start to relax with those patients according to the data you already have.

Then, as a non-dermatologist, when you say less than 50 percent of skin involvement, is that just by gross observation or do you have any more information to share with me about that?

Finally, in terms of the Phase 2 and the Phase 3 trials, 5 percent discontinued in the Phase 2 and then it was 0.8 percent in the Phase 3. What do you attribute that to? Is that due to your algorithm? Thank you.

DR. KAUFFMAN: Yes. I'll ask Dr. Singhal to come up. But to your last question, yes. We believe that the difference in discontinuation of all drugs is in fact the algorithm. Since in Phase 2 we recommended all three drugs be stopped,

in Phase 3 we refine that so that telaprevir is stopped for mild to moderate rash and PR can continue. That was not the case in Phase 3. We just didn't have enough experience with rash at that point to have been so discriminating, shall we say.

Dr. Singhal?

DR. SINGHAL: With regards to your first question, severe rash in general, the 4 to 5 percent of subjects who experienced severe rash across the Phase 2 and 3 program, about two-thirds of those at least were reported as being severe at the outset. And then about 30 percent were reported -- 30 to 35 percent were reported as being progressive rashes. So this was progressive grade 1 to grade 3, and also progressive grade 2 to grade 3. But it was a third.

With regards to time to onset, we examined this with regards to any rash as well as by grade. And as you very rightly pointed out, about 50 percent of all rashes that occur on telaprevir combination treatment occur in the first 4 weeks.

And if you break that down, as I showed with the Kaplan-Meier earlier today, they really occurred -- many of them start occurring in the first week.

However, rash has been noted at any point until the 12-week period. But the median time to onset of a severe rash is approximately 7 to 8 weeks. So 50 percent of them can occur after week 7, which is a reason to be vigilant up to the end of the dosing period.

With regards to your second question about body service area, I just wanted to reinforce that the body surface area, when we spoke of the 50 percent body surface area, we meant involved body surface area. So not just by saying that if the trunk is involved, you have some rash on it -- it's not tantamount to 18 percent, for example, by the Burns Rule of Nines. It should be really the entire trunk being involved to be counted as 18 percent.

However, because our derm expert panel noted that investigators tended to overestimate rash body

surface area, and we would want to prevent patients from unnecessarily stopping telaprevir, we are giving this special consideration in the educational documents that we are creating.

So our plans are, and they're currently underway, to create illustrations of body surface area, to have photographs that will enable prescribers to distinguish 50 percent from localized or from above 50 percent.

DR. MCGOVERN: And just one quick thing. Are you going to have a patient handout at the time you give out the prescriptions, if this drug is approved today, that physicians can give out to patients so that they understand the issue of rash?

DR. KAUFFMAN: Yes. We do plan to do that. We sort of have in mind a starter kit that would include information like that when patients get their first prescription.

DR. CARGILL: Thank you.

Dr. Van Dyke?

DR. VAN DYKE: My question was already addressed. Thanks.

DR. CARGILL: Excellent.

Dr. Ellenberg?

DR. ELLENBERG: Yes. My question was just asked.

DR. CARGILL: We're zooming here.

Dr. Murata?

DR. MURATA: I'm just simply requesting a clarification.

I understand from the sponsor's consultant, Dr. Stern, that there were a number of biopsy specimens that were submitted for outside consultant review. Were such skin biopsies of rashes mandated by protocol or performed at the discretion of the site investigator?

DR. KAUFFMAN: I'll ask Dr. Singhal to discuss that.

DR. SINGHAL: For purposes of the Phase 3 program, this was a very specific requirement. And if I can elaborate further, there were three Phase 3 trials. The ADVANCE study, which was in treatment-naive subjects, required all patients to have a dermatology consult with a rash that

required discontinuation or was grade 3 or severe, to have a dermatology consult at the site as well as have photographs taken, which were stored in a central repository, and have a skin biopsy performed with four unstained slides.

Then those unstained slides were sent to a central histopathology at the Beth Israel Deaconess here, who was part of our derm expert panel, who stained those slides and read them and gave us his consistent, sort of central read on every single biopsy. That was for study 108.

From study 108, we had about 56 subjects who experienced an event of special interest. And from those, we collected biopsies in 37. So we did have a substantial number.

Now, in addition to that, we also collected all biopsies that were collected or performed for 111 and C216, which were not stained by our central reader but were read and read out by him, bringing it to a total of about 82 biopsies.

DR. MURATA: So if I can just ask for one further clarification.

Given those numbers and descriptions, what percentage of the Phase 3 studies actually received the biopsies?

DR. SINGHAL: What --

DR. MURATA: Those who met the criteria for a dermatology consult?

DR. SINGHAL: Yes. So in the Phase 3 program, the event of special interest, so a rash that was grade 3, serious or causing discontinuation of any drug, was reported in about 7 percent of all subjects. And from those, we received biopsies of close to 70 percent of all of them.

DR. CARGILL: Thank you.

Ms. Dee?

MS. DEE: Hopefully this will be quick. The one-dose kidney impairment study, do we know what happened with that? It seemed like there was a question in the briefing document as to whether that would be sufficient.

DR. ROBERTSON: Yes. We did have a question, and a lot of it had to do with the dose

proportionality and linearity and time-dependent PK, which is a little different for telaprevir. But upon further discussion, discussion with the sponsor and some internal analyses, we're content with the single-dose study, and we believe it can be dosed full dose in all stages of renal impairment.

MS. DEE: Great. Thanks.

The other thing that was very puzzling to me, in your briefing document on page 11 it talked about illicit drug users, and it mentioned the interaction with methadone and said that 11 illicit drug users were in Phase 3. I can't believe there were only 11.

Am I misunderstanding something about that? It said, because of these methadone interactions, they were careful about allowing drug users into the trial, but they did allow 11 in. In other words, is that possible, that only 11 drug users were in all these Phase 3 trials?

MR. FLEISCHER: Well, it was a pretty strict exclusion criteria, unfortunately, and it

was -- I'll tell you what we found.

So, basically, "Subjects abusing illicit drugs, narcotics, or a controlled substance, or alcohol, or who had a history of illicit substance or alcohol abuse within two years of prior screening were to be excluded; unless subjects who had a history of abuse of illicit drugs or alcohol and an incidence of abuse within two years prior to screening, or subjects who had a history of abuse of narcotics or other controlled substances, known by the investigative site and considered to be a good candidate, were allowed in."

So that's why -- essentially, those 11 got in because they appeared to be good candidates for going onto a clinical trial. Unfortunately, the rest were excluded.

MS. DEE: So in the discretion of the investigators, all these people that were in these trials, people that were off drugs for a two-year period, only 11 were considered reliable enough to be in these trials?

I guess I should ask you that.

DR. KAUFFMAN: The inclusion/exclusion criteria, it was obviously up to the investigators to decide who to enroll in the trials among those patients on stable methadone who were considered good candidates that were not excluded, and the 11 are those that were chosen by the investigators to enroll.

DR. CARGILL: Thank you. We're going to continue.

Dr. Clay?

DR. CLAY: Convince me the statement, "This drug is not approved for use in people with gout," doesn't need to be in your package insert. I didn't see any interaction studies with gout medicines. Colchicine is no longer available, and you used it -- well, the investigators used it to treat. So convince me that doesn't need to be in your package insert.

DR. KAUFFMAN: Sorry. Could you just repeat the first part about --

DR. CLAY: Sure. "This drug is not approved for use in people with gout." It's not approved

for the use of hepatitis C in people who have gout.

DR. KAUFFMAN: Yes. I think that, you know, as you saw, there are some elevations of uric acid. I think that would really be something that would be left to the investigator's discretion or in the future prescriber's discretion as to what the potential risks are.

DR. CLAY: So is your drug safe to use in people who have gout?

DR. KAUFFMAN: We don't have much experience with it in the clinical trial, so I can't really specifically answer that question.

DR. CLAY: Okay. Thanks.

DR. CARGILL: All right. We will now proceed to our break. We will return here at 2:40. It's not going to be 15 minutes; it'll be 10 minutes -- yes, I'm being the Scrooge -- 2:40, so that we can proceed directly to the questions.

Again, a reminder to the panel: You may not discuss this meeting topic among yourselves or with members of the audience.

(Whereupon, a recess was taken.)

DR. CARGILL: We will now begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate except at the specific request of the panel.

Before I proceed further, I'd like to ask Dr. Birnkrant to make a few remarks.

Charge to Committee

DR. BIRNKRANT: I want to thank the committee for their challenging questions and their discussion. We greatly appreciate that.

Before we go to the questions, I just wanted to remind everyone that we would be most appreciative if you would refrain from comparing the two products that have been discussed over these two days. So today we're focusing on telaprevir. Thank you.

Discussion/Questions to Committee

DR. CARGILL: Thank you, Dr. Birnkrant.

We are going to read the questions and then have discussion after them. Our first question is this: Rash associated with telaprevir use was

common and sometimes severe and treatment-limiting, and anemia was more frequent and more severe in patients treated with telaprevir.

Please comment on the safety profile of telaprevir, focusing on the increased frequency and severity of rash and anemia when telaprevir is added to pegylated interferon and ribavirin. Do these adverse events affect your risk-benefit assessment, and if so, how?

I'm going to take the chair's prerogative to ask Dr. Bigby to speak first.

DR. BIGBY: Yes. Thank you very much. I just wanted to clarify a couple of things about what has been referred to as severe skin reactions.

So SJS and TEN, like I said before, are similar conditions. They generally occur in -- one case in something like 250,000 to a million exposures. In the case of this drug, you've seen two, maybe three cases in Phase 3 trials that had around 2,000 people. So it's much more common than in drugs in general.

For DRESS, the data is not as good, but I'd

say it's somewhere in the order in general of a case in 5- to 10,000 exposures. And again, with this drug you see 10 or 11 cases in Phase 3 trials of about 2,000 patients.

The third thing is that I actually was given a list of the reactions and the descriptions. And an additional severe reaction that wasn't mentioned yesterday in our discussion is AGEP, which is acute generalized exanthematous pustulosis, which again is usually a very rare entity. And it was mentioned, I think, at least once in Phase 3 studies.

So I think you will be seeing severe adverse reactions with this drug, probably more than with many or any existing.

DR. CARGILL: Dr. Roland?

DR. ROLAND: I think it's clear that for both of these adverse events, that it does affect the risk-benefit ratio, but I don't think that the risks outweigh the benefits, at least as far as we know them right now. I would like to think a little bit more about how to try to minimize the

risks and how to understand more completely in the real world what the real incidence of especially the skin reactions are.

So I don't really know what the precedence is in a situation like this for mandated reporting, some sort of registry. I'd also like to think more about how we use 21st century communication mechanisms with a nurse hotline. So being able to send photographs, being able to have real-time expert consultation, would make me feel more comfortable.

DR. CARGILL: Thank you.

Dr. Friedman?

DR. FRIEDMAN: I have a question for Dr. Bigby. The reactions of telaprevir were compared with those of Bactrim, which is an approved drug. And I wonder how your calculated figures as to the frequency compares with what we know about Bactrim.

DR. BIGBY: Yes. I don't know how Dr. Stern could have made that statement because I think that the -- at least -- you don't usually pick up an

SJS/TEN/ DRESS signal when you do a trial of 2,000 patients. And I don't think that if you look back at Bactrim trials, you'd find it of that frequency at all.

DR. CARGILL: Dr. Strader?

DR. STRADER: I agree with Dr. Roland that these side effects do appear to be more frequent. However, I think that the sponsor was very diligent in trying to characterize the symptoms and come up with plans for monitoring patients and for managing them.

As a practicing hepatologist myself, I think that I would not be terribly concerned about the management of these things. I think it is important, though, that we somehow make sure that -- with respect to the rash, that dermatologists may be involved. If there's some concerned, 21st century communication notwithstanding, I think it's better to actually have your eyes on the patient as opposed to being sent a photograph. But I think it's important that perhaps that happened, but I do not think that

these would preclude my saying that the drug should probably be approved.

DR. CARGILL: Thank you.

Dr. Van Dyke?

DR. VAN DYKE: Yes. My concern is that rash is obviously common enough that I think clinicians are going to see it regularly. And my concern is that they will begin, over time, to not appreciate the potential concern that the rash may have. So I think it's going to be really important to keep reinforcing the message to clinicians that although it's very common, it can also be very serious.

Another drug, abacavir, comes to mind. This is a drug we use for HIV therapy that is commonly used. And I think the message there is that there's a hypersensitivity reaction that occurs with every challenge that is extremely serious.

I think that message has gotten out pretty well. I think that's a good example of a situation where there is a very serious, life-threatening adverse event that could easily be overlooked with the way we manage most drugs in this day and age.

And I think a concerted effort was made to get that message out, and I think it's worked very well.

So I think there is an example of how to do this, but I think it's going to take a lot of education of providers as well as patients to make them appreciate that.

DR. CARGILL: I'm going to take the chair's prerogative and jump in here as well. We also in HIV use a drug called nevirapine, and we all certainly know very well the rash consequence of that drug, which can also be severe.

So I think that it's going to require that we be vigilant and pay attention to that. But we're not unaware that in and of itself, HIV infection, as an example, can also just de novo present with a severe rash.

Dr. McGovern?

DR. MCGOVERN: All the points I was going to make have been made. Thank you.

DR. CARGILL: Dr. Ghany?

DR. GHANY: Yes. I agree with everything that's been said by the other speakers. I am

concerned about the risk of the rash and the anemia.

But I'd like to just reflect a little bit about when we first started using interferon and ribavirin, hepatologists had to become psychiatrists and hematologists, dealing with depression and anemia. And we learned how to do that, but actually it took a while.

So my comment is to the sponsor. I'd strongly encourage the -- first I'd like to congratulate the sponsor on what they've done. I think they've done a tremendous job. But I would encourage them to try to disseminate the management of rash and anemia to expedite this so that we don't have to go through a very long learning process before we learn how to deal with this.

DR. CARGILL: Thank you.

Ms. Dee?

MS. DEE: A number of things have already been said. But I feel a lot better about the anemia concerns that I had. It seems like that they are manageable. I didn't see neutropenia

issues, and that made me feel fairly relieved. And the idea that the FDA confirmed that between 16 and 18 weeks, people start back to baseline was very helpful for me.

As far as the rash, it's funny. I thought the sponsor did a good job, too, in the assessment and management plan. The discontinuation rates between the second and Phase 3 trials I think is telling and important.

But I've also had one of these serious Phase 3 rashes -- I mean, stage 3 rashes. And it was interesting to me to see that the rash that I had was not near -- let's put it the other way. Telaprevir rashes are not near as serious by the pictures as the rash that I had.

So I'm more wondering about that patients be just as educated on not stopping instances where the rash may be manageable. So I think it was helpful to me to see the slides from the sponsor about what kind of educational sorts of things they're going to do to make sure that that message gets out as well.

DR. CARGILL: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: I think that it would be unusual to have an effective treatment for a chronic, life-threatening disease that didn't come with some extent of serious toxicity. I suppose there are some examples, but I think they must be rare.

I think that what we've heard today are certainly well within what we might expect for an effective treatment for a serious disease. So I think that while they contribute to risk-benefit assessment, they're not risks that overrun the benefits by any means.

I assume that the sponsor is doing/has done analyses to try and understand which patients might possibly be more at risk for the serious rashes. If there's any way to learn and understand who might be at greater risk, that could help physicians in making treatment decisions and it could also help with patient education in terms of emphasizing what to watch for.

DR. CARGILL: Thank you.

Dr. Korman?

DR. KORMAN: Just the following comments.

A clinical trial requires education and certification and has a defined protocol. Clinical practice requires only a license. So the answer to that question, do these adverse events affect my risk-benefit assessment, is it depends on how much anxiety is generated by that adverse event. And that anxiety is going to be dependent on my sense of security in managing that adverse event. And the more I understand it, the more I have real algorithms, not generalities, like good skin care. I mean, I don't know what good skin care is other than washing your face a couple of times a day with a non-deodorant soap.

So I think it's an obligation to really pay a tremendous amount of attention to the educational process, and not just by having some focus groups but by really using educational technology to make sure right up front that the management is as effective as possible so that as many patients who

need to be treated can be treated. Then my risk-benefit assessment and my anxiety level will go down; maybe not as high as being at this meeting, but you never know.

[Laughter.]

DR. CARGILL: Ms. Valbh?

MS. VALBH: Rash and anemia are of a concern, but I think that the sponsor has done a wonderful job in outlining how it was managed. And I would ask that the FDA, when they do label for this product, if it's approved, that there's tighter guidelines on how rash is managed -- and I'm talking about details, not general guidelines -- and also tighter guidelines on how anemia is managed so that in clinical practice, everybody knows what needs to happen and at what time points.

I think that the benefit of telaprevir speaks for itself, and I think that it would be a wonderful addition and hope for the patients that are not currently treated or who are previously treated and not responded.

DR. CARGILL: All right. Ms. Young? I was about to summarize.

MS. YOUNG: No. I'd just like to thank the FDA and the sponsor for designing some very good studies here that help us to determine the effectiveness and the risks.

Given the complexity of this course, I would like to measure in the end, it's how many patients completed successfully. So I would like monitoring, some kind of registry in terms of adverse events, maybe even dropout rates and such, so that this regimen can be improved over time.

Resistance also I think is worth following as we go along so that it won't affect patient treatment options in the future. Other than that, it's a wonderful addition to the regimen. Thank you.

DR. CARGILL: All right. So if I can summarize, we began our discussion of this question with Dr. Bigby giving us some background numbers in terms of how often some of these skin events that we've been discussing occur.

So, for example, in the case of Stevens-Johnson syndrome and TEN, or toxic epidermal necrolysis, we heard figures in the range of 1 in every 250,000 to a million in terms of background; in terms of DRESS, which is the eosinophilic and systemic symptom syndrome, again about 1 in about 5- to 10,000.

However, in the face that we also heard from the committee that there was an expectation that when there is a drug that's going to be coming forward for a life-threatening illness, that there would be side effects, and this would be part of the risk-benefit profile, and that while there is concern about risk, the overwhelming theme of the committee discussion appeared to be that the risk did not outweigh the benefit.

There were references made to several antiretroviral agents used in the care of patients with human immunodeficiency virus such as abacavir and nevirapine where certainly rash is not only not uncommon but anticipated, and we have learned how to manage.

I appreciate the comments from our hepatologists who say that they have had to learn how to manage neuropsychiatric disorders, with some tutoring. And I think we heard, repeatedly, messages for strong provider as well as patient education so that this can be accomplished and individuals can know exactly what they're looking for, and that this be detailed guidance as opposed to general guidance.

We're going to discuss question number 2. And I just want to say that before we discuss this, I just want to give you an overview, as I did yesterday, of our electronic voting system.

We will be using the new electronic voting system for this meeting. Each voting member has three voting buttons on your microphone, "Yes," "No," and "Abstain." Once we begin the vote, please press the button that corresponds to your vote. You will have approximately 20 seconds to vote.

After everyone has completed the vote, the vote will be locked in. The vote will then be

displayed on the screen, and I will read the vote from the screen into the record. Then next we will go around the room and each individual who voted will state their name and vote into the record as well as the reason why they voted as they did.

So question number 2 states: Considering the overall risks and benefits, do the available data support approval of telaprevir for treatment of treatment-naive and treatment-experienced patients with chronic hepatitis C genotype 1 in combination with pegylated interferon and ribavirin?

Dr. Friedman.

DR. FRIEDMAN: So considering where we started with non-A/non-B hepatitis, I think that it's a stunning achievement that we will be able to cure nearly 80 percent of naive patients and probably the same number of relapsers, two-thirds of whom will only have to take treatment for 24 weeks. We've almost completed a transformation of genotype 1 into genotypes 2 and 3, which I think is just a remarkable success story.

The other important aspect of this drug is that the protocol for using it is relatively simple, and it's familiar because what we're doing is basically using the same milestones we've used for peginterferon and ribavirin and grafting the new protocol onto that. And the drug that is causing us concern in terms of its side effects is only used for 12 weeks. And there's some wiggle room because if you have to stop it a little early, you might not sacrifice success.

So I think there are so many positive aspects of this drug, and for those of us who have been in the field, this is a very exciting moment.

Rash is not unfamiliar to people who have taken care of patients with hepatitis C. Of course, there are some cutaneous complications such as cryoglobulinemia. But ribavirin also causes a rash, and occasionally it can be nasty. So I think we actually have a head start in dealing with what will be a principal complication.

I think that not only do we have to educate ourselves and our patients, but I would enlist the

dermatology community. I find that to take care of all the complications related to peginterferon and ribavirin really requires a team effort. It's a multidisciplinary effort. And it goes well beyond the conventional subspecialists when you think about issues such as adherence, psychiatric care, drug use, and so on.

So I would line up the dermatologists to enlist their cooperation in the care of these patients. Many of us have already done that. But I really think this is a stunning success, so I wholeheartedly endorse approval of this. And I will not repeat my comments when it comes time to vote.

[Laughter.]

DR. CARGILL: Thank you, Dr. Friedman. I must say when I listen to your comments, I feel like I'm in a time warp, that I came to these meetings with one set of options, and depending on how the day goes, I'm sort of pinching myself and saying, is it really possible that I'm looking at numbers like this, because it's unbelievable.

Dr. McGovern?

DR. MCGOVERN: I'd like to comment that I think the sponsor has had a very clear presentation today. I understood the rationale for every single Phase 3 trial. There was a logical progression. The questions that were being posed were answered.

I think that, all along, they've been very forthcoming on resistance data, the drug-drug interaction data. They didn't present it here, but there was data on coinfection at an HIV meeting, and I was very grateful that they've already begun to address this and very exciting results there.

In terms of the safety, I commend them on restricting the use of EPO because we understand what the effect of telaprevir is and using dose reductions of ribavirin that we're familiar with.

In terms of the rash, again I commend them also on trying to dig in and understanding the rash. I just really encourage them to follow some of the recommendations that my colleagues here made, Dr. Roland and Dr. Strader, about having a hotline, having postmarketing monitoring, having

the patient handout that they're already planning on doing, things like that. I think they've done a tremendous job today.

DR. CARGILL: Thank you. Some of the things that were raised we'll come back to in the other questions.

So now we are ready to vote. If there is no further discussion, we will now begin the voting process. I would ask that you please press the button on your microphone that corresponds to your vote. You have approximately 20 seconds to vote. And press the flashing button -- you should have flashing buttons on your screen now -- firmly. After you've made your selection, it will continue to flash. And if you're unsure of your vote, please press the button again.

[Vote taken.]

DR. CARGILL: The voting result is as follows: Yes, 18, zero noes, and zero abstentions.

All right. I will ask you -- we'll begin, starting with Dr. Murata. If you would state your name into the record, your vote, and why you voted

as you did, please. And we will continue forward through Dr. Friedman and around.

DR. MURATA: Yoshi Murata. I voted yes. I was favorably impressed with the efficacy data, given the limitations of the existing ribavirin and pegylated interferon alone.

The safety concerns have been noted by myself and other colleagues on the panel today, but with the appropriate monitoring measures, as has been suggested by the sponsor, and with input from the committee and final decision with the agency, I believe that the risk-benefit profile is favorable for approval.

DR. FRIEDMAN: Lawrence Friedman. I voted yes.

DR. BIGBY: Michael Bigby. I voted yes because I think the benefits for outweigh the risks. And I'm pretty sure that there will be an adequate warning about the development of rashes.

MS. YOUNG: Kathy Young. I voted yes because of the added benefit of telaprevir, and it was proven with the statistics that we have.

DR. GIORDANO: Tom Giordano. I voted yes. Clearly, the benefits of this treatment outweigh the risks, and the risks are manageable. And I look forward to using this. There are a lot of patients waiting for this.

DR. VAN DYKE: Russ Van Dyke. I voted yes. I think we've now entered the era of specific antiviral therapy for hepatitis C. I think that's a tremendous advance, with future advances to come. I think along with that come challenges such as, particularly, viral resistance, which we'll learn how to deal with. But I think we're heading down a very important road.

DR. STRADER: I'm Doris Strader. I voted yes. I would like to congratulate the sponsors on a very well-done and thoughtful presentation. I would like to thank you as a hepatologist for the elegant simplicity of the regimen, taking advantage, as Dr. Friedman said, of already well-known landmarks and making the telaprevir dosing very short so that if there are any adverse events, that they can be reasonably well-managed. Thank

you again.

DR. CARGILL: My name is Victoria Cargill, and I voted yes for all the aforementioned reasons. And I specifically want to thank the sponsor for not only an elegant presentation and for clarity, but even if someone has concerns about the number, you offered people who are injecting the opportunity to have access to this, and I thank you.

DR. CLAY: Patrick Clay, and I voted yes. The benefits far outweigh the risk in this, and it is yet another step. And that's all it is. There's still a long way to go. This is a marathon, not a sprint.

DR. ELLENBERG: Susan Ellenberg. I voted yes. I think it's a pleasure to see an application where the efficacy is very clear and large and undeniable, and where the risks, while real, seem clearly to be manageable.

DR. ROLAND: I'm Michelle Roland, and I voted yes. I have some concerns that we'll discuss later about some of the specific populations. But

several times in the last couple of hours, I've gotten incredibly choked up about the moment that we're in right now for both personal and professional reasons. And I wanted to really acknowledge the community folks who are in the room.

DR. MCGOVERN: My name is Barbara McGovern, and I voted yes. I think this is a long-awaited landmark day for our patients with hepatitis C. And I want to thank the sponsor for taking on this challenge and also not only for addressing patients with chronic hepatitis C, but also the harder-to-treat patients such as the null responders and coinfected patients as well. Thank you.

MS. DEE: Lynda Dee. Yes, for all the reasons that everybody's said. You know, there's a discussion often among activists about whether drug companies should ever get As; we do a report card in one of my groups. And I can't forget about the small numbers of blacks and that 11 of illicit drug users. But I won't say that this is an A, but it's very close to it.

I'm very grateful for such clear data, for such concise rules about how to do this, such manageable toxicities. It was a great, really, really excellent application.

DR. GHANY: I'm Marc Ghany, and I voted yes, again, not to flog a dead horse, but because of all the reasons that have been said. And I too would like to take the opportunity to congratulate the sponsor on a really well-done and thought-out development program. It's made my job in approving this drug a lot easier.

MS. VALBH: Pritybala Valbh, and I voted yes, for all the reasons that everybody had mentioned. We're entering a new era, and telaprevir is a huge advancement in treating hepatitis C.

Thank you to the sponsor for a wonderful presentation. It was extremely clear. You did extensive drug interaction studies. You did not muddy the water with the use of EPO in your trial. And it was very easy for me and convincing that the efficacy was there for the treatment of these

patients.

DR. CONNICK: Liz Connick. I voted yes, for the same reasons everybody else stated. The tremendous clinical benefits outweigh the very concrete but manageable risks.

DR. KORMAN: Louie Korman. I voted yes because this is an important advance. I'm happy to take care of these patients, and I'm even happy to become a part-time dermatologist.

[Laughter.]

DR. KNODELL: My name is Robert Knodell. I voted yes. I think that the advent of direct antiviral treatment for hepatitis C will probably do for this disease what cimetidine did for the management of esophageal reflux and peptic ulcer disease.

DR. CARGILL: Thank you very much, members of the committee.

We'll now turn to our third question: Please comment on the strength of the evidence to support response-guided therapy with telaprevir in combination with pegylated interferon and ribavirin

for the following patient groups. And you see there treatment-naive and prior relapsers.

Dr. Clay? Yes, Dr. Giordano?

DR. GIORDANO: There's clearly strong evidence for response-guided therapy in treatment-naive patients. The prior relapsers' case, essentially made by the FDA, again I think that was an interesting argument but not necessarily the kind of data that is going to convince me that it's safe to use in patients.

Fortunately, however, the sponsor had Phase 2 data. And while the sample sizes were small, I think that the hypothesis and the biological plausibility are very strong. And even sample sizes of 100 patients are enough to convince me that there's enough evidence in prior relapsers that response-guided therapy is appropriate in this situation.

DR. CARGILL: Thank you.

Dr. Strader?

DR. STRADER: I agree. I think that in treatment-naive patients, there's adequate evidence

that response-guided therapy is efficacious and beneficial. What is a little bit of a departure for me is in the prior relapsers. Even though there weren't a lot of patients involved, to me it makes sense that if someone that I've treated before who had a response had complete undetectable HCV RNA at week 4 and then relapsed, that they may do this again, and that response-guided therapy in those patients may be beneficial; and, again, the FDA's very complicated explanation notwithstanding.

So I think that just in -- I would encourage you to abandon that. You know, it's very confusing. It's very confusing. I think that common-sense explanations probably work better. I understand addition, subtraction, multiplication, division, but still it's very confusing.

So I think that even though normally I like to see a lot more data involved with respect to prior relapsers, it makes sense to me that those patients would probably be very similar to treatment-naive, and I don't really have a problem concerning response-guided therapy in those

individuals.

DR. CARGILL: Thank you.

Dr. Roland?

DR. ROLAND: I have concerns about response-guided therapy in the subpopulation of treatment-naive individuals with cirrhosis. And I also have concerns about the sample size for the prior relapsers in the Phase 2 studies, which I think was closer to 52 than 100.

So not comparing the drug to yesterday but similar to the conversation yesterday, this may be a place where the label needs to be nuanced, where patients and providers together will need to make individualized decisions about what they value more, given the uncertainty.

DR. CARGILL: Thank you.

Dr. Knodell?

DR. KNODELL: Well, I would like to weigh in, in favor of response-guided treatment for prior relapsers. I think that the sponsor has significant positive data that directly relates to this question.

I did have a little -- I don't see the category up there, but my notes say that cirrhotics should be treated with 48 weeks of treatment whether they have an early or an extended rapid viral response or not. The numbers were pretty small, but at least I did make that -- or jump to that conclusion with regard to that treatment group.

DR. CARGILL: Thank you.

Dr. Connick?

DR. CONNICK: I agree with Dr. Knodell that I think that there are reasonably convincing data that the relapsers can be treated with response-guided therapy.

I also think, now that it's public information, that some of the data yesterday also support that approach in that I think there were clearer data presented yesterday showing that relapsers behaved similarly to -- when they are retreated to -- and that they can be effectively treated with shorter courses of therapy.

So, I mean, to subject those people to an

extra six months of interferon and ribavirin seems a little extreme. And perhaps closer monitoring so there's a larger group post-approval could provide even stronger and clearer data. But I think it's very reasonable.

DR. CARGILL: Thank you.

Dr. Ghany?

DR. GHANY: Yes, thank you. So I also agree with what everyone said already. I think the data is quite strong for the treatment-naive population that response-guided therapy is the way to manage that group.

I think the data is less strong in prior relapsers. My concern is really for prior relapsers who are difficult to treat, who have poor baseline characteristics, so those who are overweight, high viral load, cirrhotic, diabetic, and so forth. So I'd like to see some more studies on response-guided therapy in that particular group of individuals. But I do think for relapsers who have favorable pretreatment parameters, a shortened course of therapy is likely to yield very high SVR

rates.

DR. CARGILL: Thank you.

Ms. Dee?

MS. DEE: Most everything has been said. I think that -- not to compare yesterday's drug, but when I was reading both of these briefing documents, it became clear to me that -- I don't know. It demonstrated for me that there was a similar virologic response in relapsers with naives in that they behave in a similar way. So I think that response-guided therapy would be indicated for prior relapsers.

You know, the nuances about whether or not you have -- what your profile is, whether you're older, all the other considerations, might be something that the agency might want to put in the label.

DR. CARGILL: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: I think the data are pretty clear for the treatment-naive population. For the prior relapsers, my intuition, looking at the data,

is similar to what most people have said, that it's probably going to be okay. However, I think the data are really pretty sparse. I think we're drawing from several different sort of smallish data sets that are all kind of suggestive.

I feel like there's maybe a greater than 50 percent chance that prior relapsers can do fine with RGT, but I'm not sure it gets to the level that I would say the FDA should bless the RGT as clearly the preferred regimen in this group. I just do not think the data are strong enough.

I don't see data that suggest that it's not going to work. But I think more data would be necessary before it can be documented that this is the optimal regimen. And I would hope that this can be an individualized decision.

DR. CARGILL: Thank you.

Dr. Korman?

DR. KORMAN: I think the data are compelling for treatment-naive, and they're pretty compelling for prior relapsers. It would be a lot easier to convince a patient that's gone through 48 weeks of

therapy and relapsed to undertake therapy for 24 weeks. And I think the decision can be individualized depending on the underlying severity of the disease in that patient. More advanced disease may give you the option of treating for a bit longer.

I also like the FDA concept. I know you didn't want to use the word "model." I like the idea of past performance as a predictor of future performance, even though on all my investments, there's a disclaimer.

[Laughter.]

DR. CARGILL: Dr. Friedman?

DR. FRIEDMAN: I'm convinced.

DR. CARGILL: I'm stunned, Dr. Friedman, almost rendered speechless.

[Laughter.]

DR. CARGILL: Well, to summarize this question, I think that we heard a ringing endorsement support for using response-guided therapy for treatment-naive patients. I think the committee was very clear.

It's less clear that we have that same sort of strong endorsement. I think the majority opinion on the committee appears to be that there is evidence to support that for prior relapsers. But this is where the nuances begin. We're hearing concerns about patients who have cirrhosis. We're also hearing concerns about patients who may have other underlying characteristics that may make them have markers of concern such as increased body weight, higher viral loads, older age, and that the option of being able to have some nuance or some individualization of the therapy may be the most helpful.

I think we also heard some consistent discussion about it would be nice to have stronger studies and more data, that the data may not be as robust as we would like for this particular subset of the question.

We're moving on to question number 4: Please comment on the strength of the evidence to support a recommendation for use in specific populations, including but not limited to blacks,

African Americans, and patients with cirrhosis.

What if any additional efficacy or safety data are needed for specific populations?

Dr. Clay?

DR. CLAY: So there's two. One would be patients with gout. The other would be people with tuberculosis. The changes in mean uric acid levels in people taking telaprevir were 2.5 as opposed to 0.6 in the placebo groups. I think they need to conduct studies that are going to help us better understand if this drug can be used in people who are even being treated right now for gout because there are no longer drugs available on the market for the acute outbreak of gout.

The second group is -- and, I know, I'm driving people crazy with this -- is this tuberculosis issue I have because of the minor levels of pyrazinoic acid that you detected.

The beauty of this drug, which makes it a very eloquent drug, is that there are multiple ways for the body to break this down. One way is through the cytochrome P450 pathway. The other way

is through other pathways. When they did their pharmacokinetic studies and administered this drug, with drugs that block that cytochrome P450 pathway, they did not get appreciable or really significant increases in telaprevir, and that's great. That's because the drug was then shunted through the other pathways. It was the other pathway that then caused the metabolite, pyrazinoic acid, to be prevalent or be present.

I guess they may have already done this and we simply didn't have access to this data, but I would like to know, in the presence of cytochrome P450 inhibitors, when the pathway is shunted toward increased development of pyrazinoic acid, that there is not sufficient levels of pyrazinoic acid present such that if a person may have an untreated case of tuberculosis, that tuberculosis is not being exposed to subtherapeutic and therefore resistance-inducing levels of pyrazinoic acid.

Thank you.

DR. CARGILL: Thank you.

Dr. Roland?

DR. ROLAND: While the numbers are small for both blacks and people with cirrhosis, I think that the data are definitely adequate to suggest that there's efficacy. But I do need to really stress that I think with the previous question, that lumping all treatment-naive subgroups together and saying that response-guided therapy, that the evidence supports that, it just doesn't for the people with cirrhosis. So I feel like I need to say that again.

DR. CARGILL: Dr. Friedman?

DR. FRIEDMAN: So here the evidence isn't quite as strong as we would like it to be, or not strong at all in some cases. So we really do need more data. And specifically, I think we need to know what role IL28B testing in African Americans will play in the decision-making and in the use of response-guided therapy.

I have a particular concern about the cirrhotics who have been null responders to peginterferon and ribavirin. There we really don't have any significant data, and what little we have

suggests that there was no difference when they were randomized.

One of my colleagues was quoted in the Boston Globe this morning saying that we had warehoused those patients. I think what he meant was they're waiting in the wings for the next generation of therapy. They're sort of on a wait list. I said yesterday, we have a reservoir of these patients, and we really need to know if the null responder cirrhotics are going to response to retreatment with a three-drug regimen.

DR. CARGILL: Thank you. And thank you to the panel.

I think what we heard in response to this question -- oh, sorry?

Oh, okay.

DR. CONNICK: I brought this up earlier but wanted to mention again, people over 65 in both the naive and the experienced studies did not demonstrate great benefit. And I think that's an important question to be addressed in future studies as well, whether those populations really

do or don't benefit.

DR. CARGILL: Dr. Strader?

DR. STRADER: I just wanted to mention this again. I know this was brought up earlier about the number of African American patients in studies up front. I realize that when we're talking about marketing studies, we want to get international involvement, and so that may limit the number of African American patients that we see in the beginning. Then we end up approving a drug for the majority population, but then asking the minority population, which makes up a very large number of patients with hepatitis C, to wait until we can go back and look at them.

I think it would be a good idea to try to do that up front, especially to try to characterize patients in the U.S. who may make up a large portion of the population that we're looking at. So I just wanted to make that plug again, that we try to encourage sponsors to consider including minority patients up front as opposed to considering them an afterthought after the drug has

been approved.

DR. CARGILL: Thank you.

Dr. Giordano?

DR. GIORDANO: I'd like to second Dr. Strader's comments. And to go back to the previous question, just for the record, I did overstate the number in the Phase 2 studies. It was actually 67 participants in the Phase 2 studies where response-guided therapy was tried in prior relapsers. Of those 67, 52 were eligible by their early virologic response for short therapy, and 49 of the 52 were successfully treated with a short course of therapy. So just for the record.

DR. CARGILL: Thank you for that clarification.

Ms. Young?

MS. YOUNG: Yes. I'd like to second the suggestion for more studies in terms of the cirrhotic patients as well as the 65 and over and those who perhaps could be rescued from transplant, you know, further deterioration. I think that those would be good groups to study.

DR. CARGILL: Ms. Dee?

MS. DEE: I'm getting older by the day, so 65 is closer. And I think that it's important that -- I think Medicaid doesn't cover people over 65 for this. So I think that's an important consideration.

I agree with what Dr. Strader said. Obviously, I've said that numerous times. But I'm just really not convinced that there's anything but trends in the cirrhotics and in the people of color in these trials because I'm not sure there's just enough patients to say much of anything other than it looks like this or it looks like that.

DR. CARGILL: We'll try and summarize number 4 again. I think the FDA has heard fairly clearly from the committee several points, including needing information for several types of special populations; individuals with gout, individuals with tuberculosis. And I think that Dr. Clay gave a fairly eloquent description of why, that basically if you shunt into the pathway because you've blocked off cytochrome P450, will

this be a source of concern because of the change in levels of pyrazinoic acid?

Certainly the question for efficacy for African Americans and blacks, as well as cirrhotics, and we've heard multiple times about the need for inclusion of these populations given their over-representation in hepatitis C populations.

Similarly, the concern about null responding cirrhotics and what do the data say for them and can we do better, as well as the individuals over 65. And I would just also like to add that as we looked at those confidence intervals, I would remind you that 65 was one of the ones that crossed over zero.

Number 5. I can hear the committee sharpening their pencils since they really dug into this yesterday. So I'm on it, guys.

[Laughter.]

DR. CARGILL: Are there any other postmarketing studies you would like to see conducted to further define risks or optimal use of

telaprevir?

Dr. Van Dyke?

DR. VAN DYKE: I think a critical question is the implication of resistance. I think this becomes a huge issue when you only have a limited number of drugs, and it informs -- I think the question is about retreatment, the efficacy of retreatment, or cross-resistance to other medications, is really important.

I think it informs us in terms of who we should attempt to treat because if you're going to attempt to treat someone with a relatively low likelihood of success and therefore a relatively high likelihood of developing resistance, you need to know what the implications of that resistance is. Does it prevent any additional therapy, or does resistance actually fade and you might have an additional chance?

So I think this is one of the new challenges we have to face in this disease.

DR. CARGILL: Ms. Valbh?

MS. VALBH: I too would like to see some

more detailed studies on resistance. And then, as I said yesterday, I would like to see studies on the nonresponder population for other genotypes other than 1. I think that this product may have a place in therapy for other genotypes as well.

DR. CARGILL: Thank you.

Dr. Roland?

DR. ROLAND: Also similar to the comments yesterday, I think it's going to be very important for us to understand the effectiveness of this product in the real world, particularly looking at adherence and clinical management of rash and anemia.

DR. CARGILL: Dr. Clay?

DR. CLAY: I'm just going to kind of look over here because they may have already done it and I didn't see it. Grapefruit juice interaction studies because you're a PGP drug? Yes, those have been done?

DR. KAUFFMAN: Grapefruit juice?

DR. CLAY: Grapefruit juice; your p-glycoprotein -- because in your information that

you submitted, you talked about how your PGP was primarily in the gut and not systemically.

So I'm curious if you've looked at grapefruit juice impact of this or other uptake inhibitor studies within the gut. And if not, I would certainly recommend that to be a postmarketing. But if you've done it, that's great, and that's it. Thank you.

DR. CARGILL: Thank you.

Dr. Ghany?

DR. GHANY: Yes. The sponsor actually has a number of studies underway in populations that I think definitely need to be addressed. So, in addition to that, I'd also like to reiterate the point that Dr. Van Dyke raised, that we need to be careful about the development of resistance.

I would like to make sure that we continue -- that the sponsor continues to collect data on the evolution of resistance and the clinical implications, particularly, as Dr. Friedman raised, the null responders. And I think in this group of patients we clearly need to

individualize treatment.

In addition to that, I'd like to see other strategies developed to manage anemia and also understand the development of a rash with these agents because we don't have a clear treatment plan for dealing with -- specific treatment plan for dealing with rash.

DR. CARGILL: Thank you.

Ms. Dee?

MS. DEE: Okay. So we didn't say anything today about people with bleeding disorders, so I'd like to see some work in that arena.

As far as methadone, I know the study was done. I know also in HIV and some of the drugs, we've done work that increases the dose of methadone so that people are able to use it with HIV protease inhibitors. So I wonder if that's something that is possible with this drug.

Also, the HIV protease inhibitors, now, I know that we saw data at CROI that talked about reactions. But I think that the appropriate doses of HIV protease inhibitors with telaprevir needs to

be established. I mean, we know that we can use it with efavirenz and atazanavir with a ritonavir boost, but that's pretty limiting for people with HIV. And I think it's very important to that community to know a little bit more about how this drug works with HIV protease inhibitors and whether there can be a dose adjustment that would make it possible to use them.

Oh, and again -- I'm so sick of hearing my own self -- great sorts of studies for more information about cirrhotics and people of color.

DR. CARGILL: Dr. McGovern?

DR. MCGOVERN: I like the lineup of studies that the sponsor has listed for us earlier today. I'd like to echo the importance of studying African Americans further. I would like to see like an interaction of telaprevir with IL28, trying to see if we can use IL28 to help us decide who can get shorter therapies versus longer therapies.

I know that they are planning the BID versus TID studies. I know there's some published data by Marcellin on this. But I would also like, if they

are in the process of doing another larger study of that, if they could couple it with adherence since we know in HIV the smaller number of doses a day correlates with better outcomes. Thanks.

DR. CARGILL: Dr. Friedman?

DR. FRIEDMAN: So in addition to what's been mentioned, one thing that concerned me is the oral contraceptive issue. And I think we need to learn more about that and whether that's going to be a problem.

Another thing we haven't talked about -- and I don't know how important it's going to be; it may not be, but there are different formulations of peginterferon, and I think different formulations were used in different trials for different drugs. And they're associated with different dosing of ribavirin.

So I don't know if any of that's important, but at some point that probably ought to be addressed.

DR. CARGILL: Ms. Young?

MS. YOUNG: I think it would be helpful to

have some monitoring of the prior relapsers to perhaps come up with some protocols that will help risk stratification and benefit stratification for that group.

DR. CARGILL: Come on. You've got 20 more studies to come up with.

Dr. Korman, I knew you wouldn't fail me.

DR. KORMAN: Yes. I can always come up with something.

It might be useful to actually do a study of the educational benefit of some of these interventions to look at compliance and conformance and sustained virologic response to see if some of the approaches that are being recommended actually make a difference in terms of educating the community, because, again, you require education of clinical investigators to participate in a study. You can't require education of the clinical practitioner.

So some of these questions would be useful. They're not, strictly speaking, medical trials. But these are important in, really, effectiveness

in the community.

DR. CARGILL: Dr. Friedman?

DR. FRIEDMAN: Now, you see, Dr. Korman is a gastroenterologist. And I was sure he was going to want to study the anorectal complications of telaprevir –

[Laughter.]

DR. FRIEDMAN: -- because he does 20 colonoscopies --

DR. KORMAN: I'm becoming a dermatologist, remember.

[Laughter.]

DR. CARGILL: Okay. I think, on that note, we'll summarize. I can see it's degenerating here.

Well, it wasn't quite as robust a list as earlier. But I think that we still have a number of things for our sponsors to consider. So, again, I will say, as I said yesterday, I think you all are going to be in business for a long time, looking at this.

Studying the implications of resistance, we heard that from several panel members it's going to

be a big issue, particularly cross-resistance to other medications. I would add to that class-wide resistance that appears to be conferred by some of these agents, and also the question of retreating those who have had failures; especially who do we treat, and those who have a low likelihood of a sustained virologic response, but then may be trading that off for a higher likelihood of resistance, what does this mean? Studies on nonresponders to peg/ribavirin for other genotypes besides genotype 1.

In addition, we heard some concerns about what is going to be the effectiveness in the real world, especially when we have to look at how individuals will be asked to manage anemia and rash, which is a known side effect. Dr. Clay raised the issue of the impact of grapefruit juice and whether or not those studies have been done.

Again, more concerns about the need for more participation in studies of those who have been underrepresented and especially take a look at studies of those who have bleeding diatheses.

Certainly trying to look at the appropriate dose of telaprevir with a number of different HIV drugs, and the interaction and impact of IL28B, and will this be helpful and predictive?

The sponsor already has studies ongoing and is going to be doing more in several of these directions, but the BID versus TID dosing and an opportunity to look at adherence at that point, and does that make a difference, particularly given the experience we've had with HIV therapies.

The oral contraceptive issue has been raised before. But, then again, how does this play out in real time and what is this going to mean in terms of adherence? And I would also say in terms of how our patients respond or want to be engaged in this therapy. Monitoring of prior relapse and risk-benefit in those individuals who have relapsed.

Finally, taking a look at the educational benefit of interventions to try and manage some of the side effects, such as rash and anemia, and certainly also looking at the anorectal complications.

So I think at this point I'll give it back to Dr. Birnkrant for last words from the FDA.

DR. BIRNKRANT: Well, thank you very much. Well, given that we have such an esteemed panel, we have actually one more question before you go. Don't worry, you don't have to vote. It's okay.

But thinking about phrases we've heard based on the data we've seen over the last two days, that this a game-changer, a paradigm shift, and a new era all rolled into these drugs added to standard of care, can you comment on the impact of these drugs on current and future clinical trials with regard to standard of care or control arms?

DR. CARGILL: Dr. Clay?

DR. CLAY: I think currently, until these -- if these drugs get approved, of course, they become part of the treatment guidelines. And I think what these drugs reflect is another arm, a subgroup of a study that an individual could be randomized to. As newer drugs are moving forward, if the FDA is going to continue to mandate comparison to pegylated interferon and ribavirin,

then that is your control as of now. But moving forward, you add these newer agents in as comparator groups.

DR. CARGILL: Dr. Roland?

DR. ROLAND: What a great question. I think it depends on what the question is that you're looking at. But if you're looking at efficacy questions, I think this is going to have to be the new standard of care in a new noninferiority design.

If you're looking at a reduction in adverse events, then you're also probably looking at these being the comparator arm, whether it's a noninferiority design or a superiority design. Those are very important questions because otherwise we get presented with data that are meaningless to us, really.

DR. CARGILL: Dr. Strader?

DR. STRADER: I agree this is a very good question. And part of it I think may depend on IL28B information because if it turns out that if you're a genotype 1 person and you have a CC

genotype, it doesn't matter whether you get two or three drugs. That changes things just a little bit.

But I do think that the three drugs are the sort of new standard of care. I have to admit myself I was hoping that we could eliminate pegylated interferon and ribavirin as part of the lexicon because it is a difficult treatment and it is wrought with a bunch of side effects. But it appears that as of April 28, 2011, it's still part of the treatment lexicon, and these three drugs may be the standard of care.

DR. CARGILL: Ms. Dee?

MS. DEE: I think it's probably no longer ethical to have a PR-only arm. I think that Dr. Roland kind of alluded to that. I also think it's time for us to look at double DAA arms. I mean, I think the community's dying for that. I think we've learned a lot from HIV. We've seen in that arena that that's the way to go. And I think it's obviously going to be the way to go with this, yet another virus.

I think that it would also be important -- and I'm not sure, maybe early access. I think we scared the investigators with that term. I think they are looking at that as an HIV thing. And I think that, maybe not in pivotal trials but in conjunction with your pivotal trials, it may be a good idea to try and look at underrepresented populations or the cirrhotics and, you know, the cases that need early access, but in the format of a clinical trial as opposed to just giving it out like we did in HIV.

So I don't know if that makes sense, but I think we're going to need to hash out how we can get these drugs to people earlier but also do it in a safe way.

DR. CARGILL: Dr. Camardo?

DR. CAMARDO: Finally, there's an industry-wide question I can answer or at least have an opinion on. But this is really critical because we are always faced with what is the standard of care. And we in general -- and I see that this committee -- are always much more comfortable with

superiority efficacy studies than we are with noninferiority kinds of studies, and we seem to be becoming less comfortable with those.

So it's very hard for a sponsor to go into a program and not know that when they come to this committee, that they're going to actually have a reference that people accept, and that is really critically important. I don't have an answer for it. I just know it's a big question for us now.

Five years ago, six years ago, everybody knew what to compare the new therapies to. Tomorrow it's going to be a problem. And sometimes you have to make decisions in advance about what that's going to be and how you're going to evaluate it. But I don't feel like noninferiority is going to be everybody's favorite way to evaluate unless we can come up with some acceptable guidelines.

So it is a really important question, so I'm glad you asked that.

DR. CARGILL: Dr. Giordano?

DR. GIORDANO: I'm not sure we're ready for noninferiority yet. I think there is a lot of room

to improve in side effect profiles, and so there are certainly opportunities there.

To me, one of these approaches is the new standard of care as soon as they're FDA-approved and available. I agree. I think it would be unethical to devise a control arm that didn't include a protease inhibitor.

I also think the next thing that's going to change management is what Dr. Strader said, the IL28. We have to factor that in. And in that case, maybe you could have control arms that would spare a protease inhibitor. But, in general, yes, I think this is the new standard of care and has to be -- any trials have to take that into account.

DR. CARGILL: Thank you.

Dr. McGovern?

DR. MCGOVERN: I think most of the things I was going to say have already been covered. Yes, I agree that this will be the new standard of care. I agree that we have room to go in terms of side effects. There is also going to be probably different dosing intervals that will be offered by

other drugs. I agree that prospectively we should be looking at IL28 and how it factors in. So I'm just summarizing all those good ideas.

DR. CARGILL: Dr. Friedman?

DR. FRIEDMAN: So I agree. Once approved, three-drug therapy will become the standard of care. It's going to complicate how we do trials going forward. First of all, the regimens are more complicated than they used to be.

Secondly, there's this group of HCV patients, 75 percent, that have not been identified that we're going to need to identify to get them into trials if we want to keep studying naive patients. Otherwise, we're going to enrich our studies with resistant patients, and they're going to become increasingly resistant to multiple agents. So I think it's critical that we have public health efforts to identify patients with hepatitis C.

I think the ultimate goal is to develop a regimen that doesn't include peginterferon. As problematic as the side effects are with the newer

agents, at the heart of the problem of treating hepatitis C patients is that interferon is such a tough drug to have to take. So I think, at least as an intermediate goal, that ought to be a priority.

DR. CARGILL: Dr. Clay?

DR. CLAY: So let me propose this to you. When you begin your trials, whatever they look like with the new drug, a person doesn't qualify to participate in the trial that's being assessed and that is going to be submitted for safety and efficacy because of prior treatment, but they have no other options left. You allow that individual to take part in maybe not expanded access, but a compassionate use protocol.

The benefit to the sponsor is you cannot hold them accountable for safety because, really, they're going to have such a confusing noise in their dataset that you'll never really know if the drug was doing it. But you let them take credit for the efficacy because that patient had nothing left. And you allow them the experience, just like

they do in oncology. "You know what? Let's go ahead and try it." So you give them credit for the efficacy, but you don't penalize them for the safety.

DR. CARGILL: Dr. Ghany?

DR. GHANY: Actually, most of what I was going to say has been said. But I wanted to raise two other points, and that is, some of the newer agents are going to be active against other genotypes. I don't know how you're going to factor that in because these drugs are really only -- these two drugs that we talked about yesterday and today are only effective against genotype 1. So I think that's something that the FDA is going to have to struggle with again.

I also wanted to comment about the role of IL28B. I think, with the newer drugs that are more potent, the issue of interferon responsiveness is going to become really less of an issue. And I don't think IL28B is going to factor into future treatments once we have potent combinations of DAAs.

DR. CARGILL: Thank you.

Dr. Roland?

DR. ROLAND: So your question raises another question in my mind, and this isn't my area of expertise, so I have a question to help me understand this. But are there other ongoing studies where pegylated interferon and ribavirin are currently the control arm? Because if there are, then you've got some serious ethical issues to deal with, with ongoing studies right now. Sorry.

DR. BIRNKRANT: We can end the meeting now.

[Laughter.]

DR. BIRNKRANT: Well, this is why I brought it up because we're facing this with recent proposals and future proposals. But the future is here. It's not really that far away, and we have to make some tough decisions. And that's why I wanted to get some input, so that when we go back to companies, we can state the obvious but then have the backing of this committee.

DR. CARGILL: Dr. Knodell?

DR. KNODELL: I have something that hasn't

been said that may be of some help. I think it depends on the mechanism of the drug that you're looking at. If you're looking at another protease inhibitor, then I think your comparison group has to be against this triple drug regimen.

Now, there's a fair amount of side effects associated with the protease inhibitors. If something else came along -- we'll say a polymerase inhibitor -- and had a much better safety profile, then a noninferiority trial with a lot less side effects might be reasonable.

So I would urge you, when you're thinking about this, to see whether or not -- what the mechanism. If you've got a different mechanistic drug, then a noninferiority trial may be reasonable. But otherwise, probably not.

DR. CARGILL: And the last comment will go to Dr. Murata.

DR. MURATA: I will just make a conceptual comment, in that I fully understand from the hepatologists in the panel, such as Dr. Strader and Dr. Friedman, about their comments on eliminating,

down the road in terms of interferon and ribavirin, combination therapy as at least a baseline arm.

Down the road, in my opinion, a critical study would be at what stage do you actually eliminate that arm in terms of substituting one or more new agents for the interferon and ribavirin arm? So this is essentially a conceptual wording of what Dr. Knodell explicitly said in terms of mechanism of action.

DR. CARGILL: Dr. Birnkrant?

DR. BIRNKRANT: Well, I appreciate everyone's responses. And they are basically aligned with what we were thinking, but we just wanted to get some feedback because it is an extremely important situation that we're all facing at this point in time.

I want to thank everyone for this exciting two-day meeting. I haven't been this excited at work in a long time.

[Laughter.]

DR. BIRNKRANT: Again, thank you very much. I also want to acknowledge and thank the open

public speakers. We heard you quite clearly. Thank you very much.

Adjournment

DR. CARGILL: Thank you. The meeting is adjourned, and we can all let out a collective "Woo-hoo!"

(Whereupon, at 4:02 p.m., the meeting was adjourned.)